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ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

VOL. 7 (O. S., Vol. XII) SEPTEMBER, 1933 NUMBER 3

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ANNALS OF
INTERNAL MEDICINE

VOLUME 7 SEPTEMBER, 1933 NUMBER 3

THE INTERNIST AS HIS OWN PSYCHIATRIST *

By ALFRED STENGEL, M.D., M.A.C.P., *Philadelphia, Pennsylvania*

THE TERM psychiatrist as used in the title and the following discussion is intended to indicate not only the physician's relation to psychiatry proper but also to psycho-neurology and the whole range of functional diseases and all of the disorders attributable to disturbances of the sympathetic and parasympathetic systems. All of these fields of study are so interrelated that at least from the internist's standpoint wide separation is undesirable and in the absence of a comprehensive designation I have chosen the term psychiatrist to indicate the physician's relation to all nervous and mental backgrounds of disease as well as the psycho-neurologic consequences of diseases falling under his care.

The reciprocal relations of somatic disease or disease manifestations and psycho-neurologic conditions are so important that it is unnecessary to offer any apology for bringing them to the attention of a College of Physicians and no defense is needed for saying that clinicians commonly approach their study of disease with too little appreciation of the psychiatric antecedents or consequences. With no less frequency, however, psychiatrists expend all their energies on the psychic or neurologic aspects of disease lacking either the training in clinical medicine or a proper appreciation of its significant bearing on psychiatric problems.

A closer coöperation of the two groups is essential to sound clinical medicine and more serious efforts to teach medical students the psychiatric responsibilities of the clinician would greatly widen his understanding of human disease. So far as this teaching is concerned I submit that the proper place for it is in the wards of the general hospital and that it is an important duty of clinical teachers to emphasize this aspect of general medicine.

As the limitations of this discussion will prevent enlargement on all of its aspects I shall content myself with the single statement regarding treatment, that the physician who underrates or ignores the psychic factors in disease, even the grossly organic diseases, loses an opportunity for effective treatment that would distinguish the successful from the unsuccessful medi-

* Read at the Montreal Meeting of the American College of Physicians, February 9, 1933.

cal practitioner. Internists with broad experience in the practice of general medicine need not be told that varied conditions affecting the personal or domestic life of the patient have great significance in the etiology and in the manifestations of disease, but they are on the other hand often unduly disturbed by psychiatric episodes which are but a part of the whole clinical picture.

Internal medicine, it must be confessed, still labors too greatly under the domination of the school of pathological anatomy. However greatly medicine was indebted to Virchow and the other noted morphologists for their systematizing of disease and establishing clear understandings of the anatomical basis of many conditions, it must be recognized that time has brought about great advances in entirely new directions. The contributions of chemistry and physiology in particular have established viewpoints of the dynamics of many diseases that render the older static or morphological conceptions largely lifeless. The complicated and widely distributed manifestations and effects of certain general diseases and infections push into the background of relative unimportance the limited pathological lesions that may perhaps with justification be regarded as representing the primary foci or seats of onset. A real knowledge of disease requires an understanding of the complexities of the mechanisms of adjustment that follow an initial fault and not infrequently the struggle for compensations occasions new clinical pictures that show little evidence of relation to the primary lesion, which thus becomes dwarfed by contrast. The search for organic lesions, important as it undoubtedly was and still remains, may therefore prove a fruitless method of advancing knowledge of disease. It served its purpose more largely before etiology, chemistry, and clinical physiology had reached their present-day stages of development; but unfortunately the impress on medicine was so great that the physician of today is still obsessed with the feeling that the discovery of an anatomical lesion and the naming of a disease is the end of his diagnostic labors. His whole attitude toward disease and the directions of his therapeutic efforts are dominated by this point of view, and he stands aghast at the amazing fact that forms of unorthodox treatment nohow seemingly adapted to the case, under his anatomical conceptions, sometimes accomplish practical results.

To be a little more specific let us consider one illustration. Fatigue is perhaps the most frequent and most important single cause of disease, and under its influence one local manifestation after another, often functional but often also organic in nature, may develop or there may be a simultaneous appearance of several " diseases ". Each of these may perhaps be skillfully treated as purely local conditions but when the source of trouble is uncorrected each successful local treatment may be followed by new outbreaks. Those who were fortunate enough to have known Weir Mitchell or are familiar with his contributions will not need to be told that his recognition of fatigue as a cause of disease and his practical system for its correction were his great contribution to medicine; nor will they doubt that his methods

were fundamentally adapted to restore health as well as to prevent recurrences of the same sort or of other types of disease.

Nowhere in the domain of internal medicine are the confused relations between causes, results and compensations so important as in the association of visceral or bodily diseases and neuro-psychiatric conditions. Familiar as internists are with organic diseases and despite their daily contact with the beginnings and lesser grades of psychiatric disorders, it seems a regrettable fact that they have too commonly little appreciation of the significance of such conditions and, when more marked psycho-neurotic manifestations occur, fall into a panic and look to the psychiatrist for help. This condition of things is not wanting in explanation. Psychology and psychiatry have advanced very rapidly and have grown greatly in importance. Unfortunately a veritable welter of terminology and a multiplicity of "systems" have created the impression that the field is so difficult that none but the pure specialist needs aspire even to a modest understanding. Without invading this dangerous controversial territory too deeply we may at least suspect that when groups within a certain field speak in varied vocabularies and are scornful of one another, fact and fable must be considerably commingled.

It is entirely possible for the clinician to cultivate a psychiatric point of view and unless he does so many of his greatest problems and opportunities will escape him. A properly cultivated appreciation of the fact that the causation of many conditions seemingly due to organic visceral disease may be found in neurologic or psychic backgrounds or in environmental conditions is as necessary to the trained internist as is a knowledge of the biochemical or physiologic changes which accompany certain diseases and more directly cause wide-spread results than the original anatomical defect. It is part of the clinician's routine duty to recognize and determine by appropriate tests these latter factors in disease without calling upon chemists or physiologists to point them out. In the same sense it is essential to his efficiency that his apprehensions should be alive to the neuro-psychological relationships. A broader and better cultivation of this whole field on the part of both the internist and the psychiatrist is eminently desirable, and though I have just referred especially to the internist as falling short of his responsibilities may I not add with equal frankness that if experience in clinical medicine and a knowledge of the natural history of disease on the part of the psychiatrist were wider and sounder, considerable parts of his systems and credulities might be eliminated. Without enlarging upon the psychic aspects of the etiology of disease which have been so greatly emphasized in recent years, often as if they represented new discoveries, it may suffice to say that much recent literature presents quite old and good wine in new bottles. The psychogenic nature of symptoms, functional disorders or even of organic disease was not unrecognized by sound clinicians of the past even as far back as Sydenham.

A distinguished physician of the psychiatric type, but a sound clinician

besides, presented before this College a proposal that the psychiatrist of a hospital should accompany the physician in daily rounds and while he very properly indicated the advantage of this to the clinician and the patient I would beg to add that the wider horizon of the psychiatrist resulting from such an arrangement would be not the least of its benefits. One of the major diseases of medicine at the present day is the fulminant character of specialism. All admit it, yet few seek earnestly to correct it. That a more prolonged exposure to intimate contact with disease in the capacity of a general physician is a desirable foundation for specialism is as true of the neuro-psychiatrist as it is of any other specialist; and it may be added that closer association of those whose responsibilities lie in the broad field of general medicine with such specialists as the psychiatrist cannot but prove helpful to both.

However the result is accomplished, my purpose here is to emphasize the fact that a very keen psychiatric point of view is essential to the clinician, particularly because it is a part of his day's work to encounter in far greater abundance the multitude of interrelationships between organic disorders or diseases and neuro-psychiatric conditions, than can possibly occur in the experience of the psychiatrist occupied mainly with the advanced stages of such conditions. With more alert appreciation of such interrelationships the physician would himself solve many of the difficulties of functional disease and organic neuroses and would be more prompt in recognizing the initial stages of the more serious psychiatric cases eventually requiring the management of a specialist.

Analyze the problems confronting you in the medical wards of a hospital or suggested by the patients presenting themselves during a single session of a busy practitioner's consulting room and you will find psychiatric factors of importance in a very large proportion of all the cases studied. The physician unmindful of these facts gropes about for evidences of organic disease in all kinds of visceral neuroses and unfortunately by reason of the accuracy of modern methods often finds enough to satisfy his mind though he has not come at all near to the real solution of his patient's difficulties. It would prolong this discussion too much to attempt even an outline of the relations to visceral neuroses of purely psychic influences left as residues of former life, of environmental conditions, of well founded or unfounded fears, or of the relations of disorders of the sympathetic and parasympathetic mechanisms, and of pathologic endocrine glands. The whole constitutes a complicated and far-reaching chapter in the study of human disease, demanding tolerant consideration of a variety of view-points. Attempts to create new systems which would explain everything by one or another of the newer methods of approach are not more but perhaps rather less trustworthy than the old system of relating everything to pathologic anatomy.

The physician psychiatrically minded will not only appreciate the varied backgrounds of visceral neuroses and functional disorders but he will be

attracted to a closer study of the neuroses or psychoses that attend many of the definitely organic diseases with which he has daily contact. Action and reaction are here by no means always equal. A neurosis (or psychosis) secondary to an organic disease may quite overshadow the cause which gave the occasion for its occurrence. Dealt with promptly as a problem of organic disease and effectively treated, such a neurosis may readily be controlled but if allowed full development may so conceal the original cause that the physician or psychiatrist cannot well avoid a misinterpretation and misdirect much of his management. Whether seen in their earlier or their later stages such cases require a physician with a psychiatric view-point or a psychiatrist with more than ordinary clinical training.

Serious or established psychiatric problems in disease often require for their solution not only a definite point of view but more painstaking and commonly more prolonged investigation than the general clinician is disposed to give to them and also a cultivation of the technic of such investigation which he does not possess. My argument is not directed to an ignoring of the important rôle of the psychiatrist but only to emphasize the necessity of a keener appreciation of psychiatric factors on the part of the physician and a less restricted psychiatric view-point on the part of the psychiatrist.

Not to prolong my discussion too greatly let me very briefly refer by way of illustration to some of the psychiatric problems which the clinician encounters in common diseases and which he should be prepared to meet. Sometimes the cases referred to pass out of the physician's care to that of a psychiatrist, but the milder types rarely do so and are therefore possibly less familiar to psychiatrists than to internists. A much greater number of conditions might be assembled but the purpose of this discussion will be served by mentioning a few of the diseases which fall under the care of the internist and in which psychic disturbances sometimes become important features.

1. *Pneumonia.* In the late stages and beginning convalescence of pneumonia, not infrequently after the temperature has become normal, more or less complete mental imbalance, disorientation, agitation, fear, rambling, etc. produce the effect of severe mental disorder that may continue for days and even stretch into durations of weeks. I have often been called upon to see patients in this condition because grave doubts have been entertained regarding the mental future of the patients. The type of such cases is more commonly of an active agitated sort than depressive and in two at least when momentarily unobserved the patient rose from his bed and leapt out of a near-by window. The mental state of the patients under discussion differs essentially from that of the pneumonia case having active delirium during the continuance of his fever and acute disease. Unlike the latter his attention may be aroused and his appreciation of his surroundings may momentarily or for brief periods be commanded but his responses are disordered and incoherent. Left to himself the patient may carry on a rambling senseless talking, sometimes interspersed with laughing or grimacing or in other cases with sudden outcries suggesting fear or pain.

The picture presented is one of acute mental disease and the question of possible encephalitis arises though there are no objective symptoms to indicate its presence.

While this type of disease is usually of short duration in cases of pneumonia terminating without further pulmonary or pleural complications, it may sometimes last for weeks and in complicated migratory pneumonias and cases followed by empyema may extend to even greater duration.

The prognosis when the patient recovers from the pneumonia itself has been in my experience invariably favorable.

2. *Typhoid Fever.* Post-typhoidal psychoses are more prone to assume a depressive type than the pneumonic and have in some instances in my experience been followed by a change of character constituting in effect a chronic psychosis of mild degree. Hemiplegic and monoplegic conditions are occasionally met with during the course of typhoid and from the manner of their occurrence and clearing up as well as from the fact that vascular thrombosis is a frequent complication in this disease, it may be suspected that cerebral thrombosis may be the occasion of such occurrences as well as of typhoidal psychoses. Records of such thrombosis found at autopsy have been published by Curschman, Osler, Welch and others. It seems probable, however, that in transient psychoses of mild character and those appearing early in the disease (even earlier than positive diagnostic evidences of typhoid fever have come to light) less pronounced cerebral changes or purely toxic effects may be responsible for the symptoms.

3. *Septico-Pyemia.* Long drawn-out general infections falling under this inclusive heading are occasionally accompanied by psychic derangements that so greatly alter the usual symptomatology as to raise the question of mental derangements or focal intracranial disease. Occasionally the mental symptoms occur late and outlast the evidences of active infection. I recall instances in which cerebral abscess was gravely considered and operation discussed but in which the whole cerebral aspect of the infection cleared up completely without any later definite justification of even a diffuse encephalitis as the cause of the psychosis. As in pneumonia, and perhaps to a lesser extent in typhoid, it would seem that the cerebral symptoms are toxic rather than in a gross sense organic.

The cerebral manifestations of rheumatism may be cited in this same category but are so well known that it is unnecessary to discuss them here. "Cerebral rheumatism" occurs as a part of the acute stages of severe rheumatic infection and not as a sequel of the disease.

4. *Cardiac Psychoses.* The occurrence of neuroses and psychoses in cardiac disease, though it has frequently been made the subject of medical studies, is not as generally recognized by physicians or neuro-psychiatrists as its importance merits. The neurotic constitution as well as the frail physique and often the somewhat infantile condition of women or less often men with pronounced mitral stenosis developed in early life is less emphasized than it should be. Not infrequently such cases have been regarded

wholly from a neurologic or nutritional angle and the underlying factor of circulatory disease overlooked. Less often but nevertheless more than a few times have I encountered cases of rheumatic aortic regurgitation in early life, so camouflaged by neurotic manifestations that the circulatory trouble was wholly ignored.

It would be lacking in broad perspective to believe that cardiac diseases of these kinds might not operate merely as excitants of neuroses due to other causes, but there are some, and I believe not merely few, that are caused directly by the circulatory derangement.

The same types of heart disease may sometimes cause psychoses of more serious nature but my experience has been that these cases more often result from luetic aortic regurgitation and aortitis or chronic myocardial disease in later life. To what extent the luetic or arteriosclerotic changes in the cerebral vessels may contribute to the development of these cases might be worthy of consideration, but in some at least the suddenness of onset without warning suggests a circulatory explanation of cardiac origin. One or two instances may suffice:

An old servant who had had aortic regurgitation without marked symptoms and no history of decompensation suddenly while at work became violently agitated and deranged and seizing a bottle of carbolic acid drank its contents accomplishing her suicide. No previous mental disturbance and no immediate cause for her actions accounted for the happening.

An old man about 60 with luetic aortic regurgitation but no previous medical history of consequence (no great circulatory disorder and no decompensation) was sitting on a park bench with an older friend and relative whom he was visiting after a separation of years. They were reminiscing and enjoying a happy conversation when suddenly the younger man without any cause whatever rose, began to berate his old friend and became violently excited. He remained in this condition more or less and never quite fully recovered his previous entire sanity up to the time of his death a year later. This suddenness of development of the psychic disturbance, while not the rule, has at least been not infrequent in my experience, especially in the more severe forms. I shall refer to something of the same sort in connection with cerebral arteriosclerosis.

5. *Cerebral Arteriosclerosis.* The psychology of cerebral arteriosclerosis is a chapter in medical symptomatology worthy of much more extensive exploration from the standpoint of the clinician than has ever been given to it. In 1908 I presented a brief discussion of this topic before the Association of American Physicians and though it would be easy to extend that discussion in the light of subsequent experience, it is perhaps unnecessary to attempt this here. My neurologic colleagues of that day were little inclined to lay much emphasis on the cerebral circulation as a factor in neuroses and psychoses and several of them expressed the feeling that mine was a somewhat exaggerated viewpoint. It is rather interesting to me to recall that of those who entered into the discussion the one who most fully sus-

tained my contentions was an internist of wide experience—Abraham Jacobi. I should not now recall this matter of a quarter of a century past except to emphasize that in the intervening time various sorts of cerebral conditions are more commonly recognized by neurologists as due to cerebral arteriosclerosis, and classifications of psychiatric conditions at the present time are not lacking in emphasis placed upon this etiologic factor.

Physicians who have had the continuous care of old people will find no difficulty in remembering repeated occurrences, perhaps over a period of years, of cerebral episodes in the symptomatology of such patients similar to those which I reported and which I now briefly recall. Disturbances of memory, of orientation, of character; transient aphasias, motor weaknesses, emotional instabilities, somnolence or protracted wakefulness, hallucinations and transient delusions and a great variety of additional symptoms of the same order enter into the symptom picture of sclerotic old age. More striking cases are those with convulsive attacks, complete stupor or protracted deep somnolence sometimes clearing up as quickly as they developed. Often the senile patient passes from one to another phase and clouds or clears so suddenly that one can hardly believe that any other explanation than a sudden change in cerebral circulation could account for the rapid changes. One is reminded of the swift occurrence of syncope and its prompt relief.

However much we may recognize all of these symptoms as possible results of failing or disturbed cerebral circulation, when face to face with the actual case grave suspicions of more lasting cerebral disease are certain to enter our thoughts. A few type cases may suffice to indicate the major manifestations.

An old lady under my observation almost daily from the age of 80 to the time of her death at 86 passed through periods of deep somnolence to almost complete coma lasting from one to several days and repeating themselves at intervals of some months or occasionally after shorter periods of time. There was no definite history or evidence of organic disease beyond the gradual increase of the manifestations of advanced age. Specifically no indications of kidney disease or focal brain disease ever presented themselves. The terminal event was a protracted period of gradually deepening stupor and death.

An earlier feature of her case was the occurrence of symptoms of marked gastric disturbance—attacks of extreme nausea, anorexia, and regurgitation or vomiting—coming on periodically without cause or explanation. She was so convinced that a grave organic disease of her stomach occasioned these attacks that she asked to have an autopsy after her death.

A complete autopsy revealed no organic lesions nor any significant changes other than diffuse and somewhat pronounced arteriosclerosis. No focal lesion in the brain or visceral disease of any substantial character was found.

A man of 80 and upwards passed through a succession of illnesses of somewhat protracted character each of which was characterized by profound

prostration, mental aberration, somnolence, stupor, and even coma without any indications of a focal brain disease. Between these attacks, which severally lasted from one or two to two or three weeks, he exhibited merely the evidences of advanced old age with feebleness as the outstanding feature but without any indications of exceptional mental senility. There were perhaps four of such attacks before the termination of his life in his ninety-fifth year.

An instance showing the rapidity of development and the equal rapidity of recovery from marked mental disorder was shown by a quite sclerotic man of 65 who, after a somewhat heavy meal, became suddenly unconscious or at least stuporous. Attempts to rouse him having failed, his physicians were summoned but were unable to discover any cause for the condition in which he was found. At the end of forty-eight hours he awoke suddenly to complete consciousness, spoke to members of his family in his room, wondering why they were surrounding him, and was thereafter as well as he had been for years before. No recurrence of this type of disturbance occurred subsequently. Nothing was discovered to connect his attack with what he had taken at his last preceding meal which was of ordinary food but perhaps a little too abundant.

6. *Gout.* That preceding, during, or after severe attacks of gout mental disturbance sometimes occurs is a familiar statement in medical literature.

Two such instances may be recalled because in each of them the mental features of the case were so pronounced that they had occasioned consultation with psychiatrists who were gravely concerned regarding the mental future of the patients. In one of them it was frankly the opinion of the psychiatrist that a terminal mental state had been established.

The first of these patients was a woman of 55 who had long been suffering from chronic gout but who on this occasion was passing through a rather severe articular gouty attack involving chiefly her knees. There was high fever, extreme pain, and the other usual features. No excess of medication could be regarded as having contributed to the mental symptoms that occurred. Beginning with what appeared to be ordinary delirium not unlike that of any other fever, the patient passed into a state of mental disturbance of pronounced character persisting with unabated intensity when the temperature fell to lower levels and even disappeared. This condition lasted for several weeks before it gradually subsided and complete mental clarity was restored.

The second case was similarly a woman who had suffered with gouty arthritis of rather acute character terminating in a more subacute condition which after some weeks' duration and after the more acute symptoms had largely subsided, gave place to a mental condition that became extremely disturbing to her family. The patient was alert, wide awake, but completely disoriented and constantly talkative. After a period of ten days or two weeks, her relatives, particularly a physician belonging to her family, sought the opinion of a psychiatrist who was quite convinced that the condition was

a hopelessly established mental state. She, however, gradually cleared up and remained in perfect mental health up to the time of her death some years later.

In neither of the above cases were large doses of colchicum, salicylates, opiates, or other drugs of that character given at the time of or just before the development of these mental symptoms, and it did not appear probable that drugs in any way contributed to the symptoms observed.

7. *Drug Effects.* It is unnecessary to say much regarding the effects of the more powerful hypnotics and narcotics when freely administered but it is worthwhile to recall to the minds of internists the fact that the very moderate use of such drugs and even of far milder ones like bromides, when given continuously, at times produces alarming mental effects. No great difficulty arises in cases of patients under the regular attendance of physicians and nurses, though we are all at times slow in realizing that medication rather than other causes is responsible; but the occurrence of mental symptoms in patients who on their own responsibility have continuously taken, though not perhaps in large doses, some form of hypnotic often proves highly confusing.

It is unnecessary for me to attempt here to assemble the names of the drugs which in my own experience fall in this category, but it may very truthfully be stated that books on psychiatry could properly include a greater number of drugs among the causes of toxic psychosis than is anywhere recorded.

8. *Nephritis.* Kidney disease is admitted among the visceral causes of neuro-psychiatric manifestations, especially when hypertension, arterial disease, cardiac disease and uremia are associated and I shall not pause to dwell on this part of the subject. There is, however, another aspect of the relation of disease of the kidneys to psychic disorders that is not so commonly recognized and may therefore merit consideration. This is the occasional development of somewhat pronounced cerebral disorders in patients suffering from slowly developed renal insufficiency with a resulting subacute or chronic uremia. Such patients at times develop a variety of mild disorders of affective type or loss of acuity, memory and other intellectual faculties that may quite over-shadow any other evidences of the underlying cause. One case of the sort in my own experience was notable because of the sudden onset of major symptoms. A lawyer, known only to his family to be failing in vigor and mental alertness, suddenly during an address to the court stopped short in his speech, was unable to continue and utterly lost his memory of self or surroundings. Rapidly developing evidences of kidney disease and eventual death in uremia followed in a few weeks.

9. *Anemia.* Psycho-neurotic symptoms in prolonged secondary anemias and perhaps more especially in pernicious anemia are sufficiently emphasized in discussions of these conditions but it is less generally stated than may be warranted that in occasional cases the nervous or psychic manifestations so over-balance the apparent evidences of the real disease as to cause confusion in diagnosis. The psychasthenic and confusional states, occurring in such

patients when pallor and other ordinary evidences of anemia are wanting, as they occasionally are, readily create the impression of nervous or mental disorders of other sorts.

It is of course evident here as throughout the whole of this discussion that thorough-going clinical examination of all such patients and not merely a survey of their outstanding manifestations is the proper safeguard against mistaken diagnosis.

Neither the clinician unfamiliar with the neurologic aspects of medical diseases nor the psychiatrist untrained in clinical medicine can properly evaluate the present state and future of such patients or arrive at a reliable opinion of the immediate prognosis. Least of all shall we obtain assistance from those who admit no backgrounds of causation for unusual types of psychic or even physical illness except subconscious states, ancient impressions, complexes and the like. With all respect for earnest workers in such fields, let us hope that they may manifest more appreciation of clinical medicine than some of them have shown, just as we hope that clinicians shall cultivate a more active interest in psychiatric points of view.

Finally let me add that internists generally should take a broader view of their responsibilities in the study and treatment of disease than has become customary in recent years. Physicians of earlier times, unsupported by specialization, often exhibited a wider point of view and it is not an unmerited criticism of modern medicine to say that in delegating to specialists the entire management of conditions in which certain localized types of symptoms have arisen, the physician not only neglects his proper duty to the patient but, as similar experiences repeat themselves, narrows his horizon of appreciation of the whole picture of disease.

THE CEREBRAL CIRCULATION*

XXV. REMARKS ON CLINICAL PHYSIOLOGY

By STANLEY COBB, M.D., *Boston, Massachusetts*

IT WILL be universally agreed that blood must go to the brain if the human organism is to function mentally and physically. It is, therefore, important to know all possible facts about the cerebral circulation—in what ways it resembles circulation elsewhere in the body, and in what ways it differs. It may be stated at the beginning that all nerve cells of the central nervous system are easily injured by lack of oxygen. This sensitiveness to anemia is most marked in the most highly integrated centers, e.g. the nerve cells of the cerebral cortex. The cells of the more automatic bulbar ganglia withstand more anoxemia, the ventral horn cells of the cord even more, and the sympathetic ganglion cells are most resistant of all.[2] As compared to the cells of most other somatic organs, however, even these (ganglion) cells are hypersensitive to lack of oxygen.

The hydrodynamics of the cerebral circulation are unique. The brain is in a virtually closed box and is supported by a water-jacket of cerebrospinal fluid. This is not only a jacket, but fills the ventricles and perivascular spaces as water fills a sponge. The pressure of this fluid is subject to great and frequent changes. When a man lies on his side with his head at the level of his horizontal spinal canal, the fluid pressure in the whole system is normally about 150 mm. of water. Immediately on sitting up, however, the pressure within the cerebral ventricles falls to *minus* 30 or 40 mm. of water, while that in the lumbar sac is increased to 300 or 400 depending upon the length of the cranio-vertebral canal. Now intracranial venous pressure is always practically the same as cerebrospinal fluid pressure and rises and falls with it.[3, 4] Thus great changes in venous flow must be continually taking place within the skull, and the capillary circulation (which is the important area because it is here that the nerve cells get their oxygen) must compensate for or withstand more changes in blood flow and more sudden changes than most other organs of the body. To keep this flow adequate there must be a control of the caliber of the arterioles and an assured strong head of pressure in the arteries. To make sure of an even distribution of blood at good pressure the "Circle of Willis" (figure 1) joins the inflowing vertebral and cerebral arteries into one system, and assures blood supply even though one internal carotid artery should be occluded. Thus it is evident that the cere-

* Read at the Montreal Meeting of the American College of Physicians, February 7, 1933.

From the Neurological Unit, Boston City Hospital, Boston and the Department of Neuropathology, Harvard Medical School, Boston, Mass.

This work was aided by the Josiah Macy Jr. Foundation.

The paper is a coördination of some clinically interesting observations made in a study of the cerebral circulation during the past five years in the Department of Neuropathology at the Harvard Medical School. The titles of the original papers so far published are given at the beginning of the bibliography.

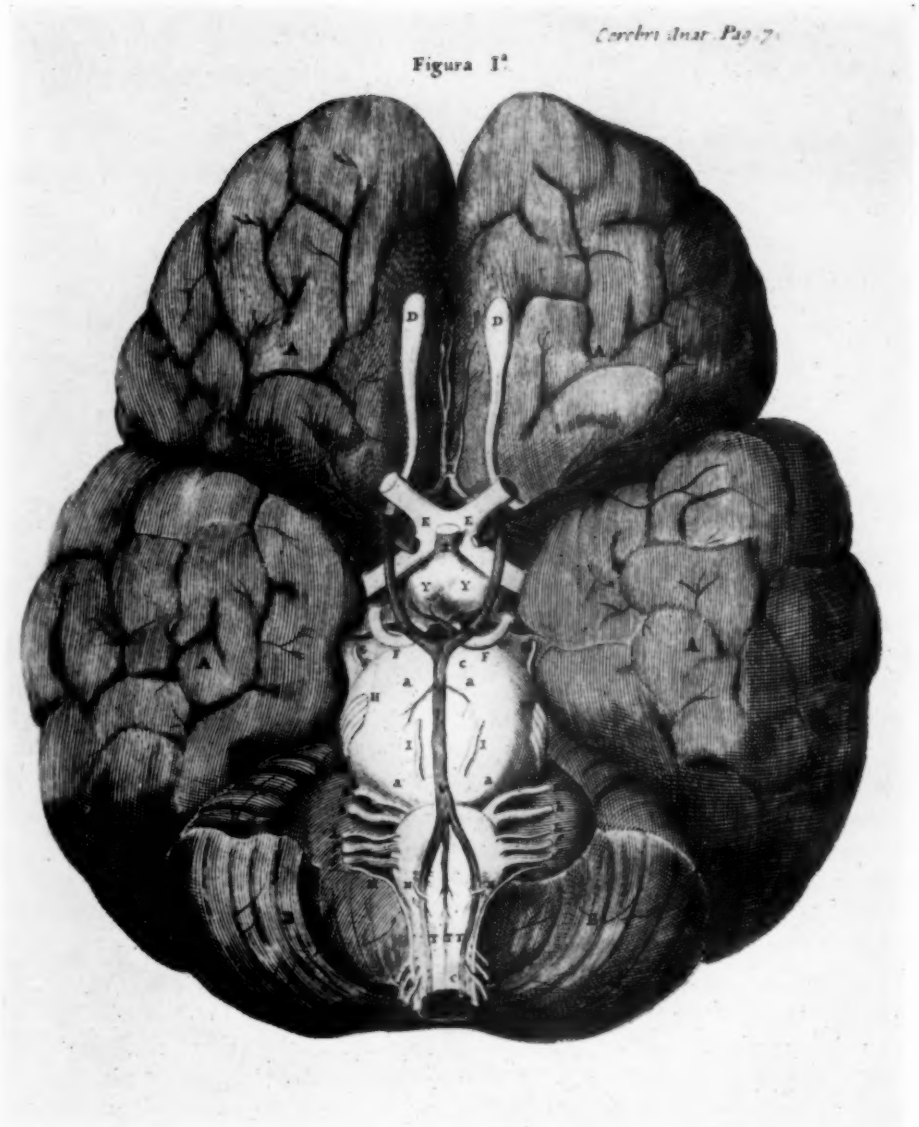

FIG. 1. Arteries of the base of the brain. (This illustration of the "Circle of Willis" is taken from Willis' book "Opera Omnia, Amstelaedami, 1682." The illustration itself was drawn by Sir Christopher Wren.)

bral circulation has some especial responsibilities and some especial mechanisms with which to meet them.

Standard and conservative textbooks usually state in regard to cerebral circulation that:

(1) The arteries are "end-arteries," i.e., do not anastomose one with another; therefore, cerebral infarct is common.

(2) There is no vasomotor control, and therefore

(3) Cerebral blood flow is regulated by the changes in general somatic blood pressure.

(4) The metabolism of the brain is low.

These statements all need examination and revision.

The Question of End-Arteries in the Brain

The idea that all cerebral arteries are "end-arteries" arose from the fact that infarcts frequently occurred in the brain and that Cohnheim in 1872 had stated that infarcts could only occur in organs in which there was no anastomosis between arteries. Anatomical studies, however, have proved that there are many cross-connections between even the larger arteries of the brain[5] and that the capillary bed (figure 2) of the brain is one great continuous network from occipital lobe to frontal pole.[6, 7] In spite of these vascular anastomoses, cerebral thrombosis does cause softening. The explanation is that relative anemia will cause nerve cells to degenerate; a complete anoxemia is not necessary.[8] When an artery is occluded the blood flow is decreased in the tissue immediately supplied, the decrease in oxygen causes the capillaries to become more permeable, edema results, and the local pressure interferes with blood coming in from the nearby normal areas by way of the capillaries, for capillary pressure is low and cannot overcome even moderate obstruction. Hence the oxygen lack is increased, the stasis becomes more complete, extravasation of red cells takes place, and a typical infarct is formed. It should be emphasized, however, that moderate degrees of local cerebral anemia can cause loss of function in the nerve cells affected without actual cerebral softening; the nerve cells simply change their reactions to certain stains, sections show areas of pallor (Erbleichung[9]), in the gross the gray matter looks slightly pale and its line of demarcation from the white matter is partially obscured. Such mild lesions are frequently all that one finds at autopsy to explain hemiplegia, aphasia, eclampsia and status epilepticus. And it should be added that few pathologists look for these mild ischemic changes. As a result many autopsies on patients suffering from these symptoms are reported as "negative." The Munich pathologists[10, 11] emphasize the importance of vascular spasm in causing such lesions, while Naffziger[12] argues that ischemia of the brain often occurs in patients with hypertension and arteriosclerosis in whom the pressure is unwisely lowered too much and too rapidly.

FIG. 2. Diagram of the circulation in one cortical gyrus. The rich capillary bed is in the gray matter around the nerve cells; it is especially rich about the large cells in laminae 3, 4 and 5. Most of the blood supply reaches this capillary network from arterioles arising from pial arteries. Thus an occlusion at "X" would cause anemia of the gray matter at "G." The number of capillaries in the white matter is much less, and they often run parallel with nerve fibers, giving the effect of an angularly branching tree, rather than a network as in the gray matter. The venous outflow is largely outward to the pial veins (shown gray in contrast to the black arteries). A small amount of blood reaches the capillary bed by way of the deep arteries in the white matter. The cerebrospinal fluid fills the arachnoid space and enters the gray matter in sleeve-like perivascular spaces.

CEREBRAL VASOMOTOR CONTROL

It has recently been clearly demonstrated that the cerebral arteries have an autonomic nerve supply; this is true of the deep intracerebral vessels as well as of the superficial pial vessels.[13] Moreover, physiological experiments have shown that there is both a vasoconstrictor and a vasodilator mechanism, stimulation of the cervical sympathetic nerve causing constriction of pial arteries, while stimulation of the vagus causes vasodilatation.[14] Further

study has shown that the cervical sympathetic nerve innervates only the ipsilateral cerebral hemisphere, but that the vagus has a bilateral effect.[15] Moreover, the pathway of the vagus impulses has been studied[15, 16] and it has been demonstrated that nerve impulses may pass up either vagus nerve trunk to the medulla oblongata, leave the medulla along both facial nerves and travel as far as the geniculate ganglion and thence along autonomic nerves to the cerebral vessels. Here they cause vasodilatation. Thus, in the brain, as in other organs of the body, there is sympathetic vasoconstriction opposed to parasympathetic vasodilatation. (Figure 3.) The stimulation of one vagus nerve causes a bilateral cerebral vasodilatation, whereas

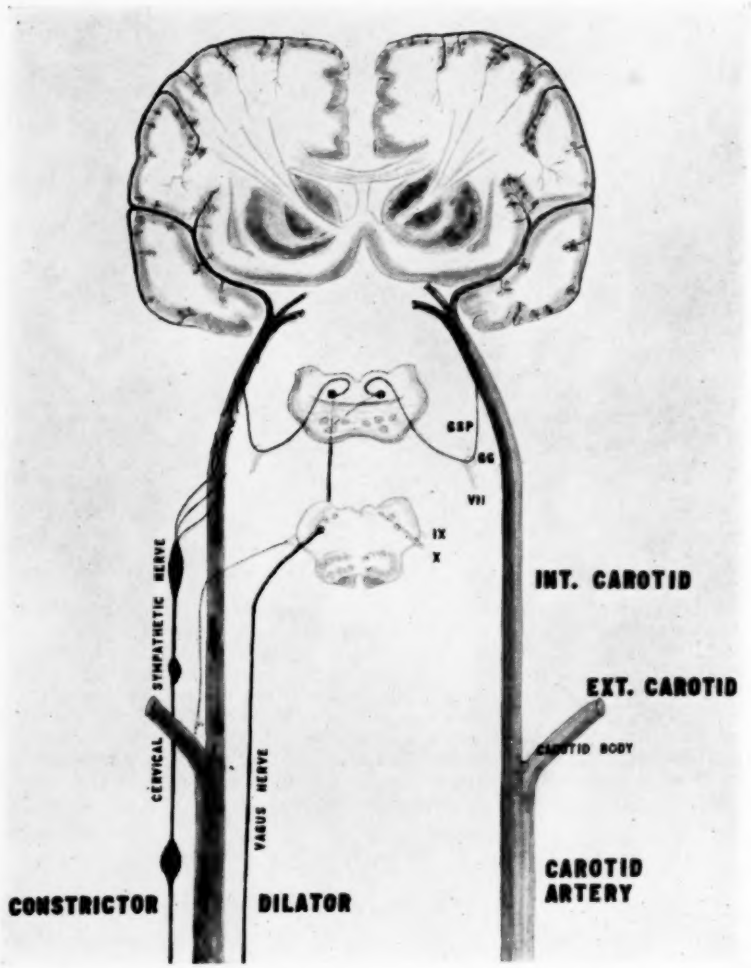

FIG. 3. Diagram of the vasomotor nerve supply to the brain. The cervical sympathetic nerve sends constrictor fibers to the carotid trunk and thence along cerebral arteries; the vagus carries dilator impulses to the medulla, which pass out along the facial nerve to the internal carotid artery and its branches. Another controlling mechanism is the nerve from the carotid body which enters the medulla with the glossopharyngeal nerve.

the stimulation of a cervical sympathetic nerve causes only an ipsilateral vasoconstriction.

Proving that the vasomotor system exists in the brain, as in other bodily organs, does not prove that it normally has an important function. Riser[17] believes that its function is negligible. Forbes,[18] who has most recently studied the question, finds that the response of the pial vessels is only about one-tenth as great as that of the vessels in the pinna of the ear to one and the same sympathetic stimulus. Putnam,[19] however, by perfusion experiments shows that cervical sympathetic stimulation causes an average reduction in blood flow of approximately 15 per cent, the systemic arterial blood pressure remaining constant.

Thus there is good evidence that the cerebral vessels contract on stimulation of the cervical sympathetic nerves, that they lose tone when that nerve is cut and that they dilate when the central end of the vagus nerve is stimulated. In other words, the blood vessels of the brain react to vasomotor impulses like vessels in other organs, but less strongly. It would seem, therefore, that partial vasomotor control of cerebral vessels is now established. How important this may be for the normal function is not yet determined, and one must be guarded in drawing clinical conclusions, but the repeated demonstration of a cerebral vasomotor system certainly makes "vascular spasm" seem to be a reasonable clinical possibility under *pathological* conditions.

Regulation of Cerebral Circulation by Distant Changes in Systemic Blood Pressure

This passive regulation of cerebral blood flow has for many years and by many authors been looked upon as the most important regulating mechanism. That such a mechanism is often effective cannot be doubted, but it should not be too greatly emphasized at the expense of other mechanisms.

Adrenalin when applied locally to the cerebral vessels of anesthetized animals usually causes a vasoconstriction[14]; when injected directly into the carotid artery, there may be a secondary vasoconstriction following vasodilatation; and when injected into a systemic vein there is usually cerebral vasodilatation. In other words, the local effect on the cerebral vessels is constriction, but this is overcome by the rise in hydrostatic pressure caused by the action of the adrenalin on the heart and systemic vessels. In the perfusion experiments of Putnam[19] mentioned above, small doses of adrenalin apparently caused constrictions of the smaller cerebral vessels when systemic blood pressure was kept constant. Until more data are available, one must look upon the effect of adrenalin on cerebral vessels as not clearly understood; probably there is a balance between local constrictor action and general systemic pressure, the resultant being modified by the state of the organism at the time of administering adrenalin (e.g., low blood pressure, anesthesia, fear, etc.).

More continuously acting and therefore more important chemical effects are those of oxygen and carbon dioxide upon the cerebral vessels. Al-

though vasomotor influences play a part in the regulation of the cerebral blood supply, more powerful control is exercised by various chemical substances in the blood stream.

Wolff and Lennox [25] observed pial vessels of cats under the microscope, and Lennox and Erna Gibbs [25] measured the oxygen content of blood taken from an artery and from the internal jugular and femoral veins of unanesthetized patients. The effect of changes in the oxygen and carbon dioxide content of arterial blood was noted in both types of experiments. It was proved that a decrease in the carbon dioxide content of the blood resulted in a moderate constriction of pial vessels in the animals, and in a decrease in the speed of cerebral blood flow in patients. An increase in carbon dioxide content was followed by a marked dilatation of vessels and an increase in blood flow. In sharp contrast an increase in the oxygen content of the arterial blood produced slight constriction and decrease in flow, while a marked degree of anoxemia showed a dilatation and increase in blood flow. Anoxemia also augmented the dilator and speeding-up effect of an increased concentration of carbon dioxide. In the human experiments it was found that changes in blood flow in the legs did not parallel changes in the brain. Oftentimes in fact, changes were in the opposite direction. The effect of carbon dioxide greatly overshadowed that of oxygen. Alterations in cerebral circulation, as measured by changes in arterio-venous differences in the oxygen content of blood, were fully as great in the brain as in the leg. The most effective measure to increase cerebral oxygen supply is the inhalation of a mixture of 90 per cent oxygen and 10 per cent carbon dioxide. The latter dilates the arteries and by inducing a condition of acidosis increases the dissociation of oxygen from hemoglobin.

Caffein (and likewise oxygen excess, alkalosis and adrenalin) is known to cause a primary cerebral vasoconstriction if given in large doses, but the reaction is modified (as with adrenalin) if the blood pressure is abnormal or if the subject of the experiment is already under the influence of other drugs.[22]

Other chemical agents that will, with regularity, cause vasodilatation (in addition to carbon dioxide and acidosis mentioned above) are histamine,[21, 23] acetyl choline, and amyl nitrite.[24] These agents evidently all work upon the cerebral vessels directly, for the vasodilatation usually takes place in the face of a falling systemic blood pressure.

Metabolism of the Brain

As long ago as 1895 Leonard Hill [26] discussed the metabolism of the brain and stated that when compared with muscle the brain is not a seat of active combustion. Recent anatomical studies bear this out [27, 28] for injection preparations of different organs show that cardiac muscle has approximately 11,000 mm. of capillary length per cubic mm. of tissue; active skeletal muscle has 6000, but at rest only 2000; the gray matter of the brain varies

from about 500 to 1000 mm. of capillary length per cubic mm., while the white matter may run as low as 200.

It has been shown [29] that the brain has a rapid blood flow in anesthetized animals, the speed being as great or greater than that of any other organ in the body (with the possible exception of the retina, which is indeed part of the brain). Calculations of the respiratory quotient of the brain have been made by Lennox [30] who compared the oxygen and carbon dioxide content of the blood drawn from an artery with that of blood drawn from an internal jugular vein, an arm vein and the femoral vein. The average of 120 observations on the internal jugular vein gave a respiratory quotient of 0.95, while 75 observations on the femoral vein gave a respiratory quotient of 0.72. Moreover, more dextrose was found to disappear from the blood in its passage through the brain than in its passage through the extremities.[30, 31] It seems from direct experiment on brain tissue [37] that the brain has a rather high metabolism when compared to other organs, or to the body as a whole.

Clinical Implications

Weiss [32] had stated that "Today when the concept of the psychogenetic origin of psychosis dominates medicine to a large extent, recognition of the fact that somato-genetic mental symptoms, personality changes and psychoses exist, and that there is some correlation between changes in the circulatory system and the mental state, is essential to the proper emphasis of psychiatry in the larger field of medicine." I would go much farther and say that everything points to the proper oxygenation of the nerve cells as one of the most vital of human mechanisms. We know little about this at present, but with new methods rapidly developing, much may be expected from the investigations of cerebral circulation. That emotional stress may play an important part in the etiology of cerebral vascular symptoms is not to be doubted. Syncope, migraine and convulsions all may be emotionally precipitated. The exact mechanisms are as yet unknown, for observations of the cerebral vessels during life are difficult. The cerebral vascular mechanism is similar to that in the skin even though quantitatively the physiological reactions differ greatly. It is a reasonable speculation, therefore, that such emotional changes as are known to occur commonly in the skin may occur in a modified form in the brain. Thus flushing, pallor, edema and serosanguinous effusions are not impossible cerebral concomitants of severe emotional stress; they all are known to occur in vascular diseases with less evanescent etiology.

Clinical evidence is abundant. The neurological effects of rhythmic changes in patients with Cheyne-Stokes respiration has been beautifully shown by Tournay [35] who found Babinski's sign present in the periods of apnea and absent when respiration was resumed. Naffziger [12] has presented a strong case for the theory that lowering blood pressure in patients with hypertension and arteriosclerosis may bring on attacks of hemiplegia and aphasia. More recently de Seze [36] emphasizes the same mechanism. I have

seen several cases where such accidents have occurred after putting arteriosclerotic patients to bed and allowing a systolic pressure to fall from around 220 to about 160, reducing the blood supply to an already poorly oxygenated brain. Moreover, pressure on the carotid sinus causes a sudden fall in blood pressure in some people, and I have seen arteriosclerotic patients in whom such a fall brought on sudden syncope with convulsive movements. The psychotic episodes of cardiac patients are common experience and may be explained on a basis of cerebral hypo-oxemia.

Vascular spasm has long been a favorite clinical explanation of brief cerebral symptoms.[33] Jackson saw constriction of the retinal arteries preceding epileptic attacks, while Foerster, Penfield and others have seen actual areas of vasoconstriction in brains exposed at operation. There are also cases of Raynaud's disease with paroxysmal cerebral symptoms.[36] Bramwell,[34] Weiss[32] and others have seen vasoconstriction in the retinal vessels at the onset of migraine. The list might be prolonged, but these examples suffice to emphasize to the clinician the practical importance of the experimental investigations upon cerebral circulation here summarized.

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THE EVIDENCE FOR A CEREBRAL VASCULAR MECHANISM IN EPILEPSY*

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THE MECHANISM of so prevalent a curse as epilepsy must necessarily interest every physician. The suggestion that vasoconstriction plays a rôle in the spread of an epileptic discharge is to be found in the prescient writings of Hughlings Jackson[1] and he himself reported vasoconstriction in retinal arteries during an epileptic seizure. Spielmeyer[2] has found histological evidence of recurring vasospasm in the brains of epileptic patients. Foster Kennedy reported visible shrinking of the brain in an epileptic attack seen at the operating table and Foerster,[3] who has observed many fits during intracranial operations, reports that the brain shrinks, then expands enormously with cyanosis of the pia. He also mentions an anemia which may spread outward from the focus.

The blood vessels of the pia mater, like vessels elsewhere, are under the control of the sympathetic nervous system as finally demonstrated by Forbes and Cobb. These vessels, moreover, have a further control, parasympathetic in type, as demonstrated by Cobb and Finesinger[4] and by Chorobski and Penfield.[5] Furthermore the blood vessels within the brain bear perivascular nerves which suggest that they too are capable of constriction and dilatation (Penfield[6]). The physiological observations which indicate nervous control of cerebral blood vessels have all been made upon experimental animals.

This is to be a report of 30 examples of epileptic seizures in conscious human patients who lay with one cerebral hemisphere exposed to view on the operating table. The immediate reaction of a practical physician to this statement may be to inquire, "Why did you operate upon these patients and what were the results?" The results so far have justified the procedure but they will not be analyzed in print until sufficient time has elapsed for reasoned judgment. There have been, so far, apparent complete cures and apparent complete failures. I shall report here only certain observations made in the course of operations, for after the opening, we usually devote an hour or two to study and observation of the brain before proceeding with any operative manoeuver.

On first seeing an epileptic patient we study him to discover whether or not his attacks have a focal pattern. If so we usually carry out encephalography. If this indicates a focal lesion and if the location of that lesion is such as to produce a seizure of the particular pattern which the patient presents we are apt to raise a large osteoplastic bone flap to inspect the brain. This done, a convulsion is usually induced by stimulation. Watching the brain during the epileptic seizures sometimes guides one to intelligent therapy, whether it be excision of a local focus, ligature of an artery or some-

* Read before the American College of Physicians, Montreal, February 9, 1933.

thing else. It has at the same time demonstrated to us phenomena associated with epilepsy which before were no more than dark conjecture.

Case I

A boy of thirteen years complained of local or Jacksonian epilepsy which affected the right hand and was often confined to that member. Osteoplastic craniotomy showed, to our disappointment, no gross lesion. I will quote from my note written immediately after operation. "Galvanic stimulation of the post-central gyrus (at 3, figure 1) near the fissure of Sylvius, produced invariably numbness of the mouth,

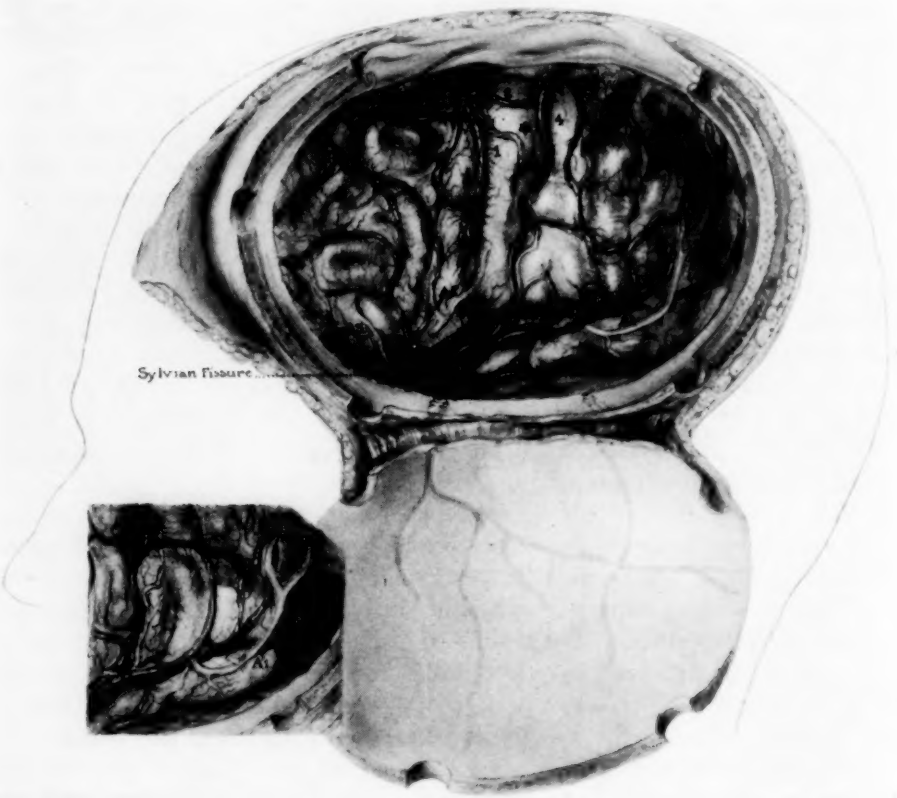

Fig. 1. *Case 1.* Left osteoplastic craniotomy. For reference to numbers see text. The pallor appeared during a seizure produced by stimulation at *x*. The inset shows the arterial constriction which appeared spontaneously after the seizure.

both sides. Stimulation of the post-central gyrus at 4 produced a clonic movement of the whole right arm accompanied by a sensation in his arm, a fact which was verified by repeating the stimulus a number of times. Movement of hand and arm were produced by stimulation of the pre-central gyrus at 1 and 2. Stimulation of the other parts of the cortex with equal intensity gave no result.

"During this exploration there were no particular changes in the appearance of the cortex. A faradic stimulus was then used just sufficient to give a twitch in the exposed temporal muscle. Various areas about the cortex were stimulated without

result and some of the large arteries were also stimulated, without result. When the post-central gyrus was stimulated faradically at point 4 clonic movements of short duration were produced as previously, but the movements went a little further, becoming somewhat convulsive in character. It was likewise noted following this that the area about the stimulation became pale. After this effect had worn off the motor gyrus was stimulated in front of this point at *x*. This resulted in a convulsion of considerable duration. During this time a zone which included most of the motor gyrus and some of the post-central gradually became quite pale, while the brain surface posteriorly and anteriorly and all the way forward to the frontal pole became red and suffused (figure 1).

"During the attack the brain was watched closely. No pulsation whatsoever could be seen in the arteries. The veins gradually became bluer and some of them almost black. The contrast between the motor area and the suffused area was striking. As the attack subsided pulsation could be seen again in the arteries, at first slightly and then with the cessation of all convulsive movements all the arteries were seen to pulsate violently.

"At this time a strange phenomenon was noted. The artery marked *A*1 showed a definite constriction. This was so sharp that it could not be doubted. The lumen was practically closed at this point (figure 1, inset). Proximal to this constriction the artery was pulsating. Distal to it no pulsation could be seen with the naked eye. There was no particular change in the color of the artery. Over a period of about ten minutes this constriction gradually passed off. At one time there persisted at the site of the previous constriction a little pallor but this eventually disappeared also.

"The initial convulsion was followed by several other wandering convulsions of different pattern. In the second such seizure, which was observed by Dr. Cone, the eyes turned, he said, in a strong, steady gaze across to the right. At the moment that this was reported we noted on the surface of the brain that a white zone had appeared in the vicinity of the artery *A*1 (see inset). The rest of the brain, even including the motor area, was now more or less suffused. This attack which was characterized as mentioned above by turning of the eyes slowly to the right, was also associated with clonic twitching of the eyelids. (The anemic zone was not far from the occipital field for eye turning.) During the next ten minutes varying areas of the brain were seen to become blanched and other areas suffused. The changes from a good color to blanching occurred in the almost imperceptible way that a cloud shadow may be seen to cross the landscape on a sunny day. Sometimes the appearance of anemia or blanching was associated with a renewed convulsion, sometimes not.

"The patient continued to have convulsions of varying types until it was deemed best to terminate them. He was then given ether. Shortly following the administration of ether the whole cortex became somewhat suffused and the motor area less pale. This made the brain become practically the same color throughout."

It is seen therefore that the above arterial constriction appeared after an epileptic seizure which involved a large part of the hemisphere. It was as this constriction was disappearing that the neighboring cortex became rather suddenly blanched. In this case blanching of cortex seems to have been associated directly with the local seizure. In other cases such blanching has appeared as a sequel to the attack.

Case II

A second case may be mentioned quite briefly. A young girl aged 18 was referred to me by Dr. Rawle Geyelin of New York. She was suffering from epileptic seizures which apparently arose first in the left hemisphere. Operation was decided upon for reasons which will not be discussed at present. An attack which was typical for her was induced by faradic stimulation of the frontal cortex, well anterior to the motor gyrus and close to the midline. Coincident with the attack the brain became

blue, the arteries stopped visible pulsation and likewise became darker. There appeared two small patches of comparative anemia just above the fissure of Sylvius. When these were noted the convulsive movements had disappeared everywhere except in the right side of the face. This continued a little longer. It was then seen that one of the two arteries which passed over these anemic areas showed a point of constriction. The convulsive movements ceased and did not return; the anemia faded.

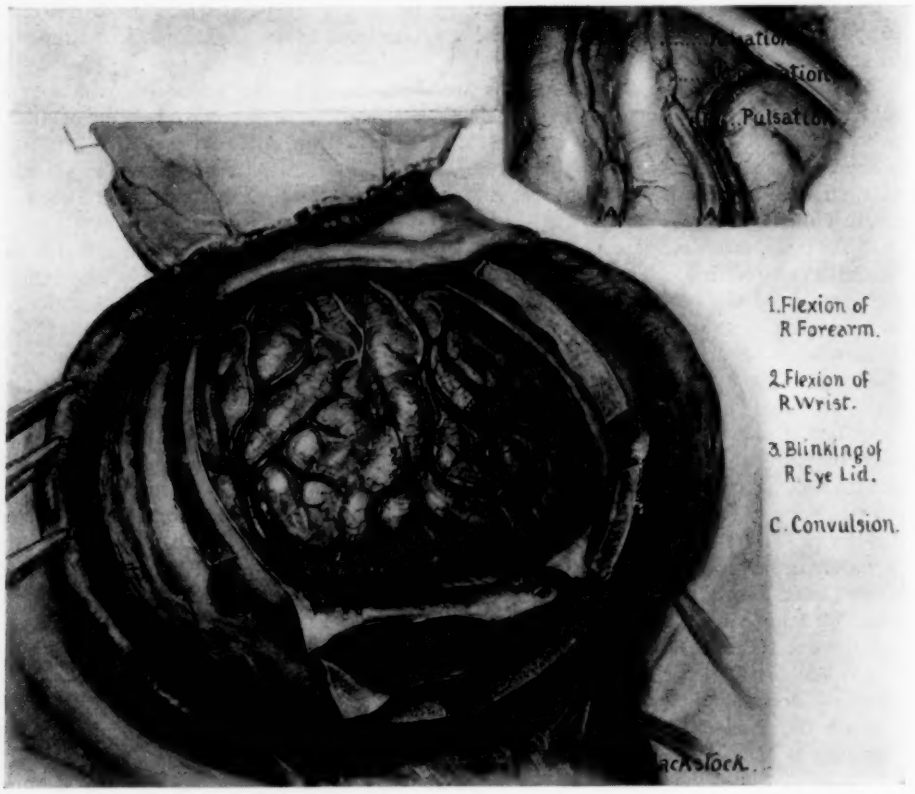

FIG. 2. *Case 2.* Left osteoplastic craniotomy. An attack was produced by faradic stimulation at point *C*. Following this the arterial constrictions indicated in the inset appeared in two arteries which originated in the fissure of Sylvius and passed upward over the cortex.

However, from then on for the next half hour these two arteries continued to show varying patterns of constriction. At one time there was a definite bologna sausage appearance in both. As indicated in figure 2 there was visible pulsation on either side of the double constriction, but not between the two constrictions.

CASE III

A young girl complaining only of recurring Jacksonian epileptic seizures on the left side of the body was referred to me by Dr. W. F. Hamilton. She was found to have an infiltrating glioma of the right frontal lobe as indicated in figure 3. After inducing a seizure by stimulation at *x* a constriction, as shown in the inset of figure 3, developed and persisted some time.

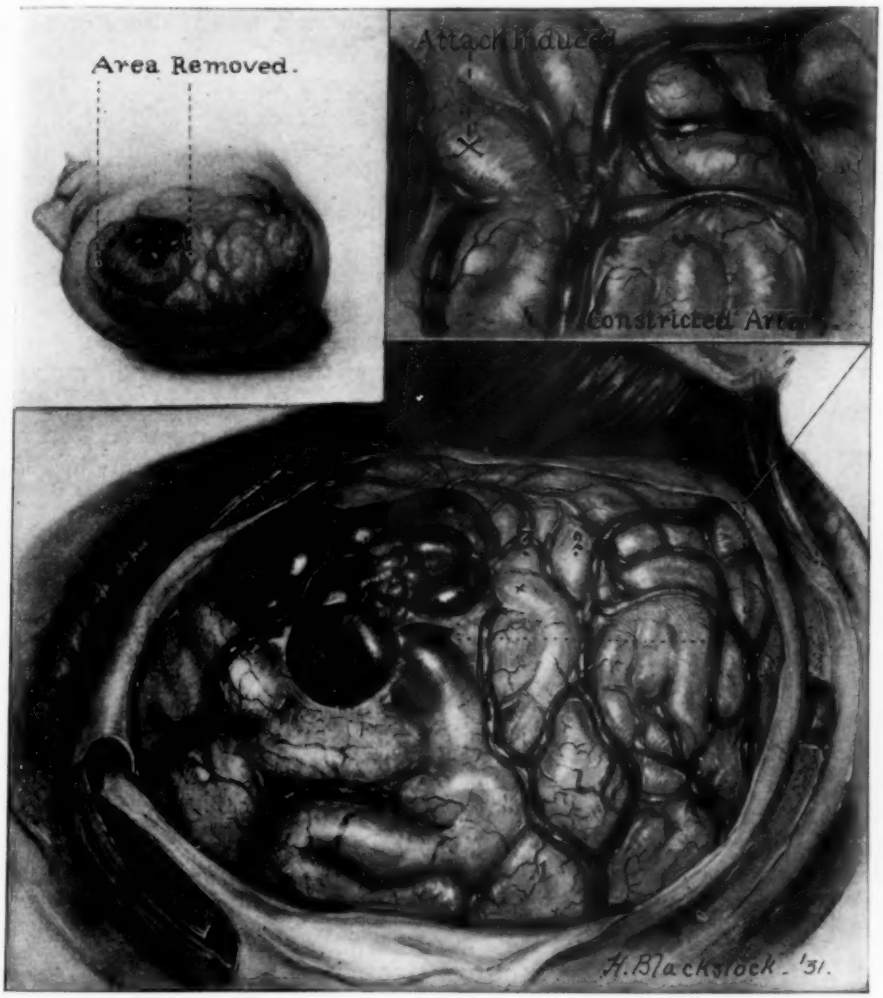

FIG. 3. *Case 3.* Right osteoplastic craniotomy. Galvanic stimulation at 1 (5 milliamperes) produced flexion of left hand, at 2 a sensation of taste (5 m.a.), at 3 twitching of the mouth. Stimulation at *x* (9 m.a.) produced an epileptic seizure. Constriction of artery indicated in inset appeared after attack.

DISCUSSION

In preparing this study I have reviewed 43 operations in which electrical stimulation of the brain was carried out. Of these cases seizures were produced in all but 13 cases.* In none of these 13 cases of stimulation without attacks did there appear arterial constrictions, areas of anemia, flushing or other vasomotor manifestations. This may serve to some extent as a control.

* Four of the failures may be explained by the fact that the site of stimulation was far frontal or occipital, sites from which we have never yet succeeded in producing a convulsion. In four cases stimulation was used only for localizing purposes.

In 30 cases stimulation was followed by an aura, a local attack or a generalized attack. In only four of these no vascular change was recorded, three being aurae only and of the other the record was incomplete. The remaining 26 cases all presented striking vascular changes and all but six showed some alteration in cerebral blood vessels or in vascularization as sequel to the attacks.

During the seizure the almost invariably associated phenomenon is the arrest of visible pulsation in the arteries of the brain, and we employ magnifying lenses to observe these vessels. This cessation of pulsation is usually wide-spread and in such cases it has been observed on several occasions that the radial pulse also disappeared completely for a corresponding period. Such a phenomenon indicates that discharge from the cerebral autonomic centers has affected the vasomotor organization of the whole body. But I do not think there is always such a generalized vascular response. In four cases the arterial pulsation was definitely reported as stopping only in a local area near the stimulation and here the seizure was, of course, a local one.

It should be further noted that stimulation caused a gyrus to blush immediately on three occasions; twice it was the post-central and once the precentral gyrus. The response on the part of the patient was slight in these cases and probably not to be considered convulsive.

In general, the arteries may become blue like the veins during an attack. If there is respiratory difficulty the veins are apt to be very full and venous pressure high, so that there occurs troublesome bleeding from various veins from which hemorrhage had been previously arrested. When bulging of the brain occurs it is doubtless due to this respiratory embarrassment. In the absence of such embarrassment I have seen the veins collapse during a seizure while the arteries became gradually blue.

Most of the findings therefore suggest that very little blood is passing through the capillary bed of the brain during the actual seizure.

Vascular Sequelae

A. Dilatation of Capillary Bed. After the attack the cerebral arteries pulsate violently and I believe more rapidly than before operation. Their color becomes a bright red and arteries which were not seen to pulsate before the seizure may now begin to do so visibly. In fact this recovery may go so far that the veins themselves take on an arterial hue. In four cases the reddening of the veins after the seizure was so marked that they approached in color the bright red of the arteries.

One extreme example of this may be cited. It was a case of focal epilepsy where we found no gross focal lesion. After extended galvanic exploration a faradic stimulus in the motor area produced a unilateral seizure. One minute later my assistant, Dr. Thomas Hoen, called my attention to a curious stripe in some of the larger veins. An amazing change had taken place. The central portion of the parietal lobe was redder than the rest of the brain. This zone was bounded by large veins.

Into the tributaries of these large veins was flowing arterial blood from this reddened zone, while into the tributaries from the outlying brain was flowing dark venous blood. The result was that the outer half of each vein was dark blue and the inner half bright red, the two streams maintaining their separation as when a muddy tributary joins a clear river and fails to mix for a long distance. When the patient was asked to cough it was noted at the Y-shaped junction of a red and blue vein that red blood was forced down a little way into a blue tributary as though the pressure resistance in the red branches was greater than that in the blue.* In such cases it must be concluded that the blood is passing rapidly through a widely opened capillary bed or that the tissues for the time being are incapable of taking up oxygen.

B. Cortical Anemia. The most frequent sequel to convulsion is not vascular dilatation but the appearance of focal areas of cortical anemia (nine cases). These may appear during the seizure but usually develop imperceptibly afterwards, indicating areas which have been the site of epileptic discharge. In one case operated upon three years ago multiple anemic spots up to 7 mm. in diameter developed upon the cortex within the general distribution of a large artery. Ligature of this artery resulted in immediate paralysis of those functions disturbed first in the inauguration and spread of his fits. The paralysis was temporary and has been followed by complete cessation of his attacks up to the present.

You are all familiar with the post-epileptic paralysis which sometimes follows a seizure and which is usually located in the involved part. This paralysis is doubtless to be explained by these associated vasomotor changes and certainly not on the basis of simple fatigue. The paralysis develops at times without a preceding convulsion. In such cases it is evidently due to spontaneous vasoconstriction. In two epileptics I have seen cortical anemia appear spontaneously.

C. Spasmodic Closure of Large Arteries. Six cases showed constriction of one or more pial arteries, a constriction which shut off the vessel completely. It may be at one point or it may extend a long distance, or there may be multiple constrictions. These constrictions remain from 15 to 30 minutes as a rule, fading out gradually.

In one case arterial constriction appeared *before* a frank convulsion but after stimulation, and in one case it seemed to appear spontaneously and without being associated with convulsion.

In conclusion, the one constant, visible phenomenon in the brain during an epileptic seizure is cessation of arterial pulsation. Pallor may be present during a seizure but more often follows it. The epileptic brain is subject to local vasomotor reflexes such as have never been described in the normal

* A word of warning may be added here. On the day following operation this patient developed aphasia and some weakness of the right side although her speech was normal all through the operation. The aphasia cleared only after two or three weeks.

Galvanic stimuli should never exceed 12 m.a. and faradic stimuli should be no greater than the weakest current capable of causing contraction in the exposed temporal muscle.

brain. These changes further cannot be reproduced in animals according to as yet unpublished work carried out by Lyle Gage in our laboratories. Physiological instability of the blood vessels seems to be the abnormal state common to epileptics of all varieties.

From the point of view of therapy the easy surgical conclusion that cervical and dorsal sympathectomy should therefore make epilepsy impossible, unfortunately does not hold. In four carefully controlled cases I carried out complete sympathectomy without abolishing epileptic seizures, although it seems to have helped one patient greatly. Gage has found the same to be true of experimental epilepsy in animals. Attacks can be induced in them even after complete sympathectomy.

The vasomotor spasms and changes seen so characteristically in the cerebral cortex of epileptics are due to vasomotor reflexes but reflexes which are probably *not* subserved by autonomic neurones placed outside of the cranial cavity. They seem to be subserved by such nerve cells upon the blood vessels of the brain and by a local vascular nerve plexus which I believe, from histological studies, to be significantly increased in some cases at least. Where such a lesion exists, excision of a focal scar with its vascular plexus is at present the most effective way of abolishing these malignant local reflexes.

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THE VALUE OF ALIMENTARY GALACTOSURIA IN THE DIAGNOSIS OF JAUNDICE*

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THE INCREASE in our knowledge of hepatic physiology has led to a multiplicity of tests of liver function. It is now possible to find reports of the most diversified methods for evaluating the condition of this organ. The activities of the liver in the metabolism of fats, carbohydrates and proteins, its power to excrete bilirubin and various dyes and its ability to store water have all been utilized for this purpose. Although it is realized that the various functions of the liver may be unequally disturbed by disease and that a single functional test may therefore occasionally fail, the necessity for the multiplicity of tests proposed has been questioned.[1] It is felt by some that we already have sufficient means to show in a general way whether or not the liver function is disturbed and that the present need is for a method of examination which will aid in the differential diagnosis of the type of disturbance which exists. Of the tests now available, one, the production of alimentary galactosuria, seems to offer definite assistance in differentiating the types of jaundice and it is with a discussion of the value of this test that this paper is concerned.

The carbohydrate metabolic activity of the liver has been studied in many ways. The production of alimentary glycosuria, the glycemic response to adrenalin, the metabolism of lactic acid, studies of the blood and urine sugar after the ingestion of levulose and galactose and, recently, the response to the combined administration of insulin, glucose and water [2] have all been utilized in a study of this aspect of liver function. It is unnecessary to consider the theoretical and clinical features of all of these tests. However, in order to evaluate the results of our studies, we will briefly review the present knowledge of galactose metabolism.

In 1899 Sachs [3] demonstrated that to remove the liver from frogs markedly lowered their tolerance for levulose although they still were able to handle glucose and galactose satisfactorily. Strauss,[4] in 1901, first used levulose to study liver function in human beings and demonstrated a decrease in levulose tolerance in the majority of patients with liver disease. This finding was rapidly substantiated by many workers and within a relatively short time the levulose test of liver function was being widely used. Within recent years, however, this test has lost some of its popularity and has now, except in England,[5] been largely superseded by the use of galactose. The use of this sugar in the study of hepatic function was first suggested by Bauer,[6] in 1906.

* Read at the Montreal Meeting of the American College of Physicians, February 8, 1933. From the Medical Wards and the Gastro-enterological Clinic of the Hospital of the Graduate School of Medicine of the University of Pennsylvania.

There is ample theoretical background for this use of galactose. Its utilization principally by the liver was demonstrated by both Draudt [7] and Fischler,[8] who showed that when the sugar is fed to dogs with an Eck fistula from 80 to 85 per cent of the galactose is excreted in the urine. Bollman, Power and Mann [9] state that the same amount is excreted by dogs whose livers have been removed. Mann and Magath [10] studied the relative value of various sugars in relieving the hypoglycemic shock caused by hepatectomy and found that the liverless animal could not use galactose. That the intestines are not necessary to the utilization of galactose was shown by Wörner,[11] who states that the tolerance toward this sugar is the same whether it be given by mouth or injected into a branch of the portal vein. Foster [12] showed that a very small difference exists between the arterial and venous blood sugars after galactose feeding, and felt that this indicated that the sugar is not used in the muscles.

The relative ease with which galactose forms glycogen in the liver has been subject to some question. Brocard,[13] for instance, felt that galactose and levulose were utilized with equal ease by the liver. Most workers, however, state that galactose forms glycogen poorly. Foster,[12] believed that the marked hyperglycemia which occurred after this sugar was given indicated that the liver had difficulty in absorbing it. Isaac and Adler [14] demonstrated by perfusion experiments that the liver does not easily form glycogen from galactose. This opinion was also expressed by Abderhalden,[15] Hofmeister [16] and, more recently, by Cori.[17]

At the present time it is generally felt that there is no kidney threshold for galactose. Folin and Berglund [18] were able to find the sugar in the urine after giving quite small doses. Harding and Van Nostrand [19] after careful blood studies, concluded that no threshold exists for this sugar; this is also the view of Blöch and Weisz.[20] This point is important because if a threshold is present, its variation would affect the amount of galactose passed by different individuals. Because galactose is very rapidly absorbed it is difficult to correlate the sugar findings in blood and urine specimens; and although it is probable that no threshold exists for galactose, this point is not completely settled. Halberkann and Kähler [21] have shown that galactose is excreted unchanged in the urine.

In discussing the value of galactose in testing liver function it is important to consider the influence of insulin on the assimilation of the sugar. Wierzuchowski [22] reported that insulin reduced the amount of galactose passed in the urine. Corley,[23] however, stated that although insulin caused galactose to disappear rapidly from the blood the degree of galactosuria was unaffected. Basch and Pollak,[24] Weltmann,[25] and Blöch and Weisz [26] also felt that insulin had little or no effect on the utilization or excretion of the sugar. The earlier work on this point is subject to some question since differentiation of the blood sugar into glucose and galactose was not done. This criticism, however, does not apply to the recent work of Roe and Schwartzman,[27] who made separate determinations of these two sugars.

They showed that even toxic doses of insulin do not change the rate of removal of galactose from the blood of rabbits and that galactose is not a direct physiological antagonist to insulin.

Theoretically, therefore, galactose, which is utilized exclusively, though with difficulty, by the liver, which is probably without a kidney threshold and the metabolism of which is uninfluenced by insulin is a suitable substance with which to test the function of the liver.

Bauer's original papers stressed the occurrence of excessive alimentary galactosuria in cirrhosis [6] and in catarrhal jaundice.[28] This was not found in cases of jaundice due to obstruction. That it is parenchymal liver damage which lowers the tolerance to this sugar was shown by Roubitschek,[29] who induced phosphorus poisoning in animals and found an increase in galactose excretion. The test was soon applied clinically and Bondi and König,[30] Reiss and Jehn,[31] Wörner and Reiss,[32] Hatiegan,[33] and others [34, 35, 36, 37] reported a definite degree of success in diagnosticating hepato-cellular jaundice by means of alimentary galactosuria. These authors agreed that the test was usually positive in jaundice due to parenchymal liver damage and usually negative in jaundice due to obstruction. Many of them state that the use of galactose gave more accurate results than the use of levulose. In 1919 Wörner [38] summarized many of the previously reported cases in the statement that excessive alimentary galactosuria was present in 80.5 per cent of catarrhal jaundice and in 6.8 per cent of obstructive jaundice. He and others concluded that a positive response to the test indicated the existence of diffuse parenchymal damage to the liver. The diagnostic value of the test, however, has not been unquestioned. Rouillard [39] stated that tolerance for both levulose and galactose is influenced by extrahepatic factors, and that tests based on the use of these sugars are unreliable. Frey [40] looked upon the galactose test as unsatisfactory, but used too small a dose of the sugar for accurate conclusions. Jacoby,[41] Faltitschek and Krasso,[42] Beckmann [43] and others reported cases of liver disease with normal galactose tolerance. However, a review of these reports indicates that even though alimentary galactosuria may be absent in many undoubted cases of hepatic damage, such as cirrhosis, severe congestion, and malignancy, these are usually cases of chronic or circumscribed liver disease and that the test is frequently positive in patients with catarrhal jaundice or toxic hepatitis. On the other hand, Althausen and Mancke [2] reported 10 cases of catarrhal jaundice only two of which were positive to the galactose test.

Some of the lack of agreement in previously published reports is undoubtedly the result of an absence of uniformity in technical procedures, such as the dose of sugar used and the length of time over which urine is collected. There has also been no universally recognized criterion for a positive result. Bauer recommended the administration of 40 grams of galactose since he found that the normal tolerance was between 20 and 40 grams and that with doses of less than 40 grams most normal individuals and many of those with liver disease would assimilate the entire dose of the

sugar. Strauss [44] found sugar in the urine only twice after 37 normal individuals had been given 30 grams of galactose. The use of a dose of 40 grams of the sugar was advised by Wörner and Reiss,[32] Blöch [45] and also by Schellong [46] who was able to demonstrate an absence of galactosuria in a case of arsenical jaundice if smaller doses were used. Reiss and Jehn [31] noted no relationship between weight and liver function and Meyer and Stern [47] found that the galactose metabolism of children is similar to that of adults. Rowe [48] has studied galactose tolerance in a large series of patients, mostly without liver disease, and feels that the tolerance to this sugar is not related to age, weight or body surface. He does feel, however, that there is a definite difference between the sexes in the ability to utilize galactose and that women have a somewhat greater tolerance than men. Rowe states that the assimilation limit for normal men is 30 grams but for women prior to the menopause it is 40 grams. This difference is ascribed to the activity of the mammary gland. A review of the cases reported does not bear out this contention of Rowe, for the amount excreted after a 40 gram dose of galactose seems entirely independent of the sex of the patient. It must be recalled, however, that Rowe's method of examination is purely qualitative and that he regards as positive the presence of sufficient sugar in the urine to cause a positive Benedict's reaction. It is not entirely accurate, therefore, to compare his results with those obtained from quantitative sugar determinations. A possible explanation for the discrepancy which exists between the opinions of Rowe and others may be found in the work of Harding and Moberley.[49] They state that women seem to have a greater diuretic response to water than do men. For that reason the urine passed by women after the ingestion of sugar solutions is more dilute and more sugar must be taken by women to give a positive Benedict's test. If, therefore, the result of the qualitative Benedict's test is used as a criterion for sugar tolerance one might be led to the conclusion that women have a greater tolerance for galactose than do men.

At the present time 40 grams is the accepted dose of galactose for the testing of liver function. As has been mentioned, Frey [40] used only 20 grams, while Hirose [50] administered 25 grams. It is obvious that results from their series cannot be compared with those obtained when the larger dose is used.

There is also some disagreement as to the period over which urine should be collected after the ingestion of the sugar. In most instances, urine contains galactose for no longer than four or five hours so that we have terminated our studies after five hours. This follows Bauer's original recommendation. Many collect the urine for two six-hour periods.[31] Fiessinger and Thiebault [51] advise examining the urine for 24 hours after the galactose is taken. Wagner [37] examined hourly specimens until two which were sugar-free were obtained. Bauer [52] has more recently adopted this method since he feels that the oliguria occasionally seen in cirrhosis may cause delay in the excretion of the sugar.

There are great differences in the degree of galactosuria which the various authors consider as a positive indication of liver disease. Schellong [46] and Wagner [37] feel that excretion of more than one gram after taking 40 grams of galactose should be regarded as indicating disturbance of hepatic function. Brugsch [53] looks upon 1.5 grams as the most a normal individual will excrete. Bondi and König,[30] Wörner and Reiss,[32] Neugebauer,[34] Davies,[54] Kahler and Machold,[55] and Sisson [35] diagnose liver dysfunction if two grams are excreted. Bode [56] and Elek and Oppenheimer [57] are more conservative and feel that patients with normal livers may excrete up to three grams. Jacoby,[41] on the other hand, did not use a quantitative test but based his conclusions on the duration of the galactosuria. Fiessinger and Thiebault [51] feel that the concentration of the excreted sugar and not the amount is important. They state that a normal individual who takes 40 grams of galactose and then not more than 1500 c.c. of fluids within the next 24 hours should pass the sugar in a concentration of 0.1 per cent or less. If hepatic disease is present the concentration may reach 1 per cent.

Such diversified standards can lead only to confusion. We feel that the most accurate and conservative diagnostic evaluation is that of Bauer who emphasizes the amount of sugar passed. He feels that the excretion of two grams or less of a 40 gram dose of galactose is normal, and such a result is considered negative. An excretion of between two and three grams is weakly positive and is suggestive of the presence of liver disease, while the passage of more than three grams is strongly positive and indicates that liver disease is definitely present. We have used this evaluation in reviewing our own cases.

In 1922 Kahler and Machold [55] recommended that a study of blood sugar response be substituted for urinary excretion in determining the galactose tolerance. They were led to do so by their failure to obtain a pathological degree of galactosuria in cases of cirrhosis. They also felt that examination of the blood sugar eliminated the renal factor which entered into the older method, since they believed that kidney disease could interfere with excretion of the sugar and cause false negative results. This last point is still unsettled. Corley [23] was unable to show any decrease in galactose excretion after producing experimental nephritis and he could not increase the excretion by causing phloridzin diabetes.

Folin and Berglund [18] have reported that hyperglycemia does not occur after galactose ingestion but this has not been confirmed. Foster [12] and Bodansky [58] showed a marked rise in blood sugar after feeding galactose to animals, the latter demonstrating that this sugar caused more glycemic response than either levulose or glucose. Kahler and Machold,[55] using the degree of hyperglycemia after galactose feeding as the criterion, reported a higher incidence of positive results in liver disease in general than was obtained by examining the urine. This opinion was also expressed by Bode,[56] Noah,[59] Jezler,[60] Kähler,[61] and Davies.[54]

Until recently, clinical studies of the blood sugar curve after galactose

ingestion were made without any attempt to determine separately the amount of galactose present. This explains the extremely variable results obtained and may also explain the frequently noted association of low blood sugar with increased urine galactose. In such cases it seemed probable that the blood glucose was lowered to such a degree that even after galactose feeding the total blood sugar remained low. Relying on the fact that galactose is much less easily fermented by yeast than is glucose, Somogyi[62] devised methods for their separate determination. These may be used in the urine when the test is carried out in a diabetic and have been applied to the study of the blood by Blöch and Weisz,[20] and Petow, Kosterlitz and Naumann.[63, 64]

Perhaps the most informative of the papers dealing in detail with the characteristics of the blood sugar curve after galactose feeding is that of Blöch and Weisz.[20] They found that in normal individuals the rise in blood sugar frequently begins within five minutes after the galactose is taken. This is too soon for the galactose to have reached the blood, and Blöch and Weisz showed that this early rise is due to an increase in glucose, which is assumed to have been reflexly released from the liver. When the galactose reaches the blood stream fifteen or twenty minutes later there is slowing up of this release of glucose or some of the glucose actually may be reabsorbed so that the total blood sugar does not become very high. When there is parenchymal liver disease the release of glucose from the liver is unchecked and since the liver is also less able to hold the galactose, marked hyperglycemia is produced. If the hepatic disease is very severe, the liver may contain so little glycogen that no glucose is released. In such a case the total blood sugar will be quite low and, since there is no threshold for galactose, we have the appearance in the urine of an amount of sugar which seems entirely disproportionate to the degree of glycemia.

The reported studies of galactose tolerance by means of blood sugar determinations indicate that this method is more accurate in diagnosticating liver disease in general, and particularly cirrhosis, than is a determination of galactosuria. It is important to note, however, that even in those papers which emphasize the value of the blood method the majority of cases of jaundice due to parenchymal liver damage show marked urinary excretion of the sugar. Indeed, Noah[59] and Elek and Oppenheimer[57] cite cases of catarrhal jaundice in which galactosuria was marked in the presence of a normal blood sugar curve. Since the blood method can hardly be said to be accurate unless a separate determination of galactose is done, a procedure rarely practicable in the average hospital, and since it offers no advantage over simple urine examination in determining the types of jaundice, we feel that there is little reason for its use for this purpose.

That pathological galactosuria can occur in patients who have no liver disease became known shortly after the introduction of this test. In 1911 and 1912 Pollitzer[65] reported patients who had marked disturbance of the vegetative nervous system and also one with hyperthyroidism whose tolerance to galactose was definitely decreased. These patients had normal

glucose tolerance. Since then pathological galactosuria has been noted in hyperthyroidism,[66, 44, 37] status lymphaticus,[52] severe asthenia,[67] marked neuroses,[44, 37] Addison's disease[68] and continued fever.[69] That some neurological factor may be involved in the regulation of the blood and urine sugars after galactose feeding is suggested by the work of Hirschhorn, Pollak and Selinger[70] and of Pollak and Selinger.[71] It was reported by them that the administration of ergotamine and atropine lowered the blood sugar curve and reduced the galactosuria. These workers felt that there is some neural or hormonal control of the liver cell activity in assimilating the sugar. The drugs, by releasing this control, increased the liver's power to utilize the galactose. Bauer and Wozasek[72] confirmed this influence of ergotamine and atropine and felt that it indicated a sympathetic stimulation of the liver to assimilate this sugar. It seems probable, therefore, that the ability of the liver to handle galactose is at least in part under the control of the vegetative nervous system. That the endocrine glands also exert some effect on galactose tolerance seems true. Rowe[73] has reported marked variability in tolerance for this sugar with endocrine disturbances. Churchman[74] has found levulosuria in patients with functional hyperplasia of the posterior lobe of the pituitary. We have seen patients with marked hypopituitarism whose tolerance for all sugars was increased and who were able to take tremendous doses of galactose, in one case up to 70 grams, without causing sugar to appear in the urine. That these influences of the nervous system and endocrine glands limit somewhat the value of the test from a liver standpoint must be admitted. While, however, the endocrine disturbances which elevate galactose tolerance might lessen the probability that coincident hepatic dysfunction would cause excessive galactosuria, they do not detract from the diagnostic value of this if it is found. It must also be realized that those glandular conditions, and notably hyperthyroidism, which cause decreased galactose assimilation may do so because of secondary liver damage. For these reasons, and because association of hepatic disease with endocrine or nervous disturbance is uncommon and should ordinarily be recognized, we do not feel that the value of galactosuria in the differential diagnosis of jaundice is greatly lessened.

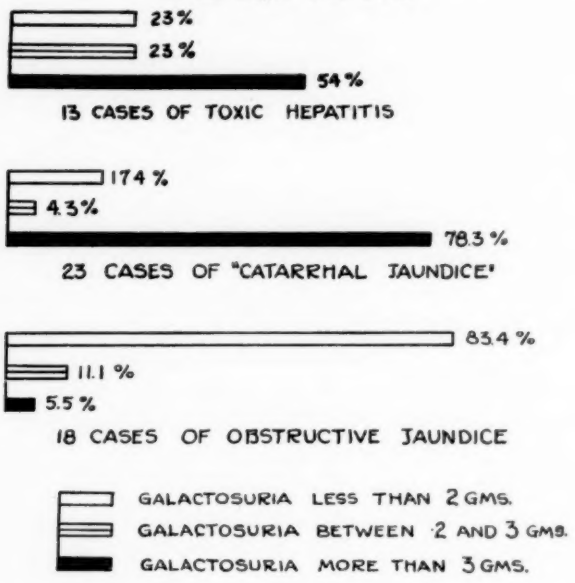
We will not enter into a detailed consideration of the clinical aspects of the levulose tolerance test. The aid which it affords in the diagnosis of liver disease has recently been stressed by Kimball.[5] In the differentiation of the individual hepatic disorders, however, levulose is not of much value. Hohlweg[75] noted marked decrease in tolerance to this sugar in experimental jaundice whether due to phosphorus poisoning or to ligation of the common duct. Strauss[76] stated that the levulose test is positive in 70 to 75 per cent of cases of catarrhal and luetic jaundice and in 62.5 per cent of mechanical jaundice. The difference in the incidence of positive results in these two types of icterus is not sufficient to be of much assistance in differentiating them.

During the past two years we have used the galactose tolerance test in

studying 54 cases of jaundice. This group was composed of 18 patients with obstructive jaundice, 23 with catarrhal jaundice and 13 with toxic hepatitis. The results of these examinations are summarized in tables 1, 2, and 3 and in chart 1. Galactosuria of three grams or more occurred in 54

CHART I

Results of the Galactose Tolerance Test in 54 Cases of Jaundice. A 40 Gram Dose of the Sugar Was Used.



per cent of the patients with toxic hepatitis, in 78.3 per cent of those with catarrhal jaundice and in only 5.5 per cent of those with jaundice due to obstruction. Although this series is comparatively small, these figures agree very closely with those of Wörner,[38] whose results have already been mentioned.

Of the group with obstructive jaundice only one patient had a definitely positive response to the test. He excreted more than three grams of galactose on two occasions. This patient had a stricture of the common bile duct with jaundice of four weeks' duration. At operation definite biliary cirrhosis was found. Two other patients, however, also had biliary cirrhosis but excreted normal amounts of the sugar so that we do not feel that this alone is a cause of decreased galactose tolerance. Two patients with obstructive jaundice had galactosuria of between two and three grams. This might be considered suggestive of liver cell damage but in both of these cases the duration of the jaundice was short and nothing was found other than the slight increase in excretion of the sugar to indicate that such damage existed. There was no correlation between the degree of jaundice and the galactose passed in the urine. Most of the cases in this group had been jaundiced for a relatively short period. In one patient, however, who had a

TABLE I

Results of the Galactose Tolerance Test in Obstructive Jaundice

	Age and Sex	Duration of Jaundice	Galactose Excretion (Gm.)	Serum Bilirubin (Mg. %)	Cause of Obstruction
1. P. M.	58 ♂	4 weeks 5 "	5.24 3.09	9.0 15.0	Stricture of Common Duct (Biliary Cirrhosis)
2. J. McB.	56 ♀	5 "	0	8.0	Carcinoma Head of Pancreas
3. L. G.	26 ♀	8 " 10 "	1.85 0.9	8.0 6.4	Cholelithiasis
4. A. D.	58 ♀	12 days	0	14.0	Carcinoma of Gall-Bladder
5. T. S.	42 ♂	1 week	0.937	1.7	Chronic Pancreatitis
6. J. K.	69 ♂	4 weeks	1.065	36.0	Cholelithiasis Carcinoma Head of Pancreas
7. C. S.	48 ♀	2 days	1.404	1.5	Cholelithiasis (Biliary Cirrhosis)
8. I. S.	50 ♀	2 weeks	1.126	10.0	Cholelithiasis
9. A. G.	46 ♂	1 day	1.336	0.3	Cholelithiasis
10. M. H.	66 ♀	Unknown	1.776	0.9	Cholelithiasis Pancreatitis
11. C. O'N.	43 ♂	5 days	0	2.75	Cholelithiasis (Biliary Cirrhosis Pancreatitis Hepatic Abscesses)
12. T. A.	50 ♀	3 weeks	1.045	2.5	Cholelithiasis (Hepatitis)
13. W. M.	24 ♂	Unknown	1.73	0.7	Cholangitis
14. F. K.	57 ♂	12 days	2.53	8.0	Cholelithiasis
15. D. T.	18 ♀	6 "	1.64	6.0	Cholelithiasis
16. B. J.	52 ♀	19 "	0.336	0.75	Cholelithiasis
17. S. H.	55 ♀	About 5 months	0	1.8	Operative Injury to Common Duct
18. A. J.	57 ♂	18 days 103 "	2.09 0.25	16.5 12.0	Carcinoma of Pancreas and Liver

partial obstruction of the common duct for about four months the galactose tolerance was normal.

Of the 23 patients with catarrhal jaundice only five excreted less than three grams of galactose and of these one patient passed 2.005 grams. The other 18 had galactosuria of more than three grams. Seven of the 13 patients with toxic hepatitis excreted more than three grams of the sugar; three of the remaining six passed between two and three grams of galactose.

TABLE II

Results of the Galactose Tolerance Test in "Catarrhal Jaundice"

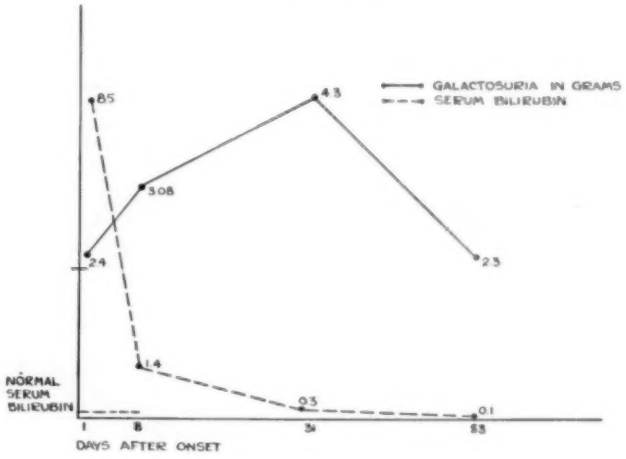
	Age and Sex	Duration of Jaundice (Days)	Galactose Excretion (Gm.)	Serum Bilirubin (Mg. %)	Wassermann Reaction
1. F. M.	27 ♂	9	5.125	6.0	Positive
2. L. L.	22 ♀	11 22	5.63 10.0	16.0 10.0	"
3. R. G.	27 ♀	11 19 36 69	4.55 4.32 4.799 2.079	15.0 3.9 0.4 0.35	Negative
4. T. N.	14 ♂	9 16 23	4.68 2.85 0	2.2 0.85 0.75	"
5. G. K.	14 ♂	9	18.08	4.0	"
6. C. L.	32 ♂	22	0.748	18.0	"
7. S. H.	50 ♀	36 52	3.95 2.29	2.0 1.6	"
8. J. P.	43 ♂	15 25 70	4.86 4.36 2.025	13.5 11.0 0.5	"
9. R. D.	29 ♀	11	2.005	6.0	"
10. E. G.	21 ♀	23	1.24	1.5	"
11. F. R.	18 ♂	8	11.0	3.0	"
12. A. R.	43 ♀	15 27	10.08 5.13	7.0 8	"
13. P. M.	37 ♀	5 49 94	3.08 6.51 4.7	2.4 0.6	"
14. D. S.	53 ♂	15	0.5	4.5	"
15. W. H.	31 ♂	7 13	14.95 2.56	7.0 5.0	"
16. I. H.	15 ♀	10	5.24	—	—
17. E. F.	31 ♂	11 32	3.35 0.288	— —	Negative
18. R. D.	29 ♀	9 29	12.011 2.855	6.0 —	Positive
19. E. G.	25 ♂	18 37	3.3 1.91	1.4 —	Negative
20. D. M.	13 ♀	6 18	3.38 2.71	2.0 0.75	"
21. E. K.	23 ♀	8 14	6.59 2.716	18.0 6.0	Positive
22. W. M.	55 ♂	15 19	6.92 2.32	13.0 7.0	Negative
23. S. R.	32 ♂	25	1.25	1.5	"

In the cases of toxic hepatitis and catarrhal jaundice there was extreme variability in the amount of galactose in the urine. This ranged from 0.147 to 18.08 grams. There was no relationship between the degree of jaundice and the galactosuria. The highest excretion, 18.08 grams (practically one-half of the sugar taken), occurred in a patient whose serum bilirubin was four milligrams per cent. The smallest amount of galactose was passed by a patient whose serum bilirubin was 12 milligrams per cent. The most severe jaundice was seen in a man who had galactosuria of only 1.017 grams. These findings emphasize the fact that the various liver functions can be separately disturbed, a point recently stressed by Cantarow.[77]

Bauer[28] and also Wagner,[37] noted that in many cases of hepato-cellular jaundice the high galactose excretion frequently persisted when the serum bilirubin had returned to normal. We noted this in some of our patients, for instance, W. R. (Chart 2.) This patient entered the hospital with

CHART II

The Relation between Serum Bilirubin and Galactosuria in W. R. Who Had Pneumonia and Jaundice.



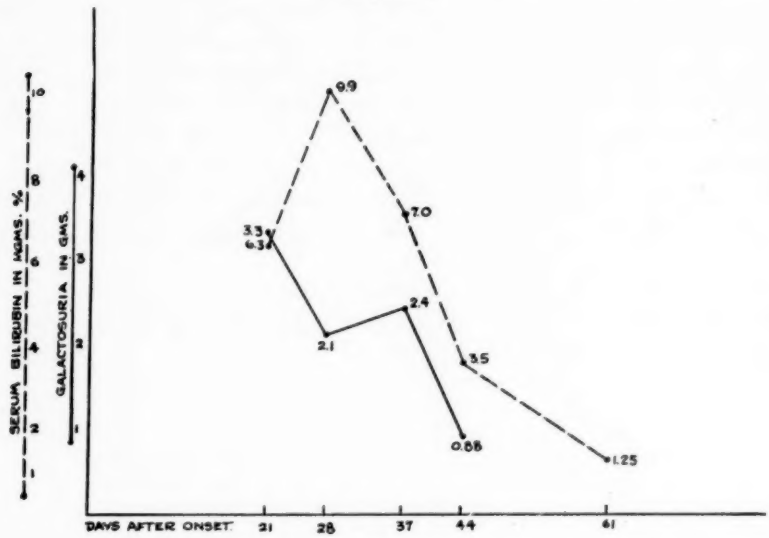
pneumonia and jaundice. Despite a rapid drop in the serum bilirubin the galactose tolerance decreased, but slowly, and at a time when the jaundice was entirely gone he still excreted 2.3 grams of the sugar. In another patient, however, the opposite picture was seen. This man, W. C. (chart 3), had arsenical hepatitis. His galactose excretion was never very high while under our observation and returned to normal rapidly. The jaundice, on the other hand actually increased and did not entirely disappear for months. These cases are further proof of the dissociation of the individual liver functions and of the necessity for using more than one test in studying this organ.

The duration of excessive galactosuria in the cases of toxic hepatitis and catarrhal jaundice was extremely variable. In some cases it was gone within three weeks. In others it persisted for very long periods, even as long as

three months. Certainly, normal liver function cannot be said to have been restored if the galactose excretion is high, even though other evidence of hepatic disease has disappeared.

CHART III

The Relation between Serum Bilirubin and Galactosuria in W. C. Who Had Arsenical Hepatitis.



In our group with catarrhal jaundice four had positive Wassermann reactions. Neugebauer [34] reported that of 22 patients with early lues but no jaundice the galactose excretion was over three grams in 15. This high frequency of decreased galactose tolerance in syphilis uncomplicated by hepatic disease has not been noted by others. We believe that the incidence of syphilis is no higher in our group than in our hospital patients as a whole. We do not feel that the lues was a cause of the jaundice in these cases, although, as Ruge [78] states, it may have made the patients more susceptible to the particular agent that causes catarrhal jaundice.

In considering the results of the galactose tolerance test in our cases of catarrhal jaundice and toxic hepatitis we were interested in determining what relationship existed between the duration of the jaundice and the results of the test. Roubitschek [29] had noted that the galactosuria that is caused by phosphorus poisoning tends to decrease if the poisoning is prolonged. He ascribed this to regeneration of the liver and resumption of its ability to assimilate the sugar. Blöch and Weisz [26] also felt that with regeneration the liver tissue regained its power to form glycogen from galactose. Althausen [79] states that the newly formed liver cells can readily maintain the carbohydrate regulating function. Other workers [80] have concluded that a high galactose excretion is always obtained in patients with diffuse liver cell damage unless the test is delayed sufficiently to permit liver regeneration.

TABLE III

Results of the Galactose Tolerance Test in Toxic Hepatitis

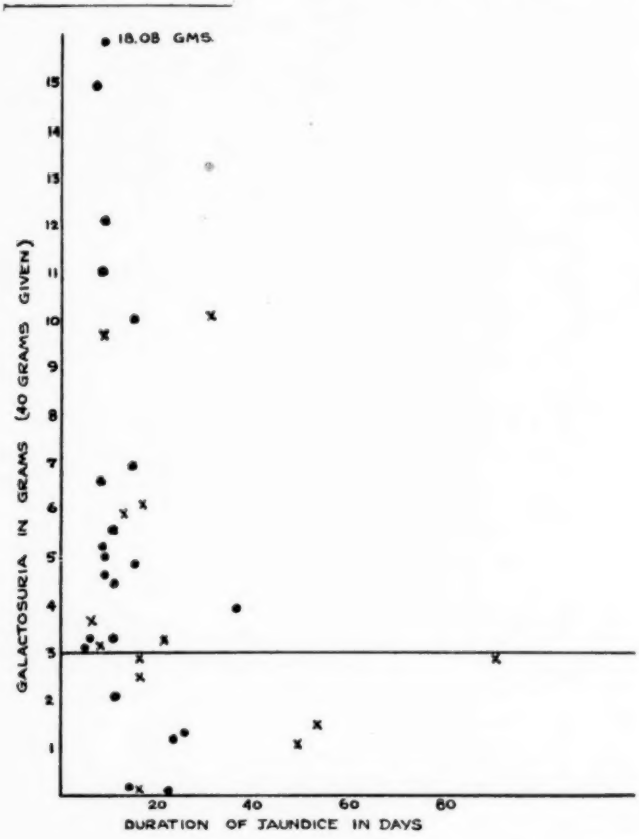
	Age and Sex	Duration of Jaundice (Days)	Galactose Excretion (Gm.)	Serum Bilirubin (Mg. %)	Toxic Agent
1. D. S.	20 ♂	16 31	2.845 2.865	4.8 0.9	Arsphenamine
2. E. M.	20 ♂	6 12 19	3.72 8.86 5.32	8.0 7.0 4.0	" "
3. W. C.	37 ♂	21 28 37 44	3.296 2.102 2.4 0.88	6.3 9.9 7.0 3.5	"
4. G. S.	31 ♂	13 26	5.85 3.48	0.7 0.4	" "
5. M. W.	47 ♀	16	2.582	10.5	"
6. S. B.	44 ♀	53	1.47	7.0	"
7. M. B.	49 ♀	16	0.147	12.0	"
8. S. S.	35 ♂	49	1.017	22.0	"
9. M. P.	64 ♀	17 20 24	6.08 2.8 1.74	— — 2.0	Cinchophen
10. R. L.	26 ♀	31	10.5	15.0	Cinchophen and Cholecystography
11. J. C.	57 ♀	9 22	9.742 3.29	3.0 —	Cinchophen
12. W. R.	31 ♂	1 8 31 53	2.38 3.08 4.3 2.3	8.5 1.4 0.3 <0.2	Pneumonia
13. V. DeL.	29 ♀	90	2.9	—	Toxemia of Pregnancy Ending in Acute Yellow Atrophy

In our 13 cases with toxic hepatitis a definitely positive result, an excretion of three grams or more, occurred in patients who had been jaundiced from six to 31 days (average 10.7 days). Definitely negative results, excretion of less than two grams, were found in patients who had been jaundiced from 16 to 53 days (average 39.3 days). If the cases with a doubtfully positive response, that is, with an excretion of between two and three grams, are included with those definitely positive, the average duration of the jaundice at the time of the galactose test becomes 22 days.

Of the 23 cases with catarrhal jaundice 18 had a galactosuria of three grams or more. The duration of jaundice in these patients varied from five to 36 days (average 11.7 days). The duration of jaundice in the five cases which excreted less than three grams ranged from 11 to 25 days (average 19.1 days). These findings are presented in chart 4.

CHART IV

The Degree of Galactosuria in Relation to the Duration of the Jaundice in 13 Cases of Toxic Hepatitis (x) and 23 Cases of "Catarrhal Jaundice" (·).



Although in both these groups the negative results were obtained in patients whose jaundice was of a longer average duration, the duration of the individual cases varied sufficiently to warrant further analysis. Since the pathogenesis of the jaundice is known in those who had toxic hepatitis, these cases will be considered separately. In this group the three negative results were obtained in patients who were first seen when the jaundice had been present for 16, 49, and 53 days. At first glance it would seem that in the last two cases the long continuance of the disease had permitted regeneration of the liver tissue and that this had restored the normal liver function. This thought, however, is not substantiated by the clinical course of these patients. One died, probably of acute yellow atrophy, the day after the galactose test was done. The other patient, a man with arsenical hepatitis, developed subacute liver atrophy with marked increase in the jaundice and tyrosin in the urine. The galactose test remained repeatedly negative. It is possible, of course, that in both of these patients sufficient functioning

hepatic tissue remained to normally assimilate the galactose. The important point is, however, that very severe liver damage can exist and the galactose test still give a normal result.

In patients with catarrhal jaundice the disease was also of longer average duration in those whose galactose test was negative. In this illness, however, the overlapping of the durations of the jaundice at the time of the positive or negative results was even more marked than in the group with toxic hepatitis. It was also noted that in some of the patients high degrees of galactosuria persisted over long periods. These facts led us to believe that duration of the disease may not be the only factor in a case of catarrhal jaundice which determines whether the galactose test shall be positive or negative.

Catarrhal jaundice is not a disease entity.* It is probable that the symptom complex that goes by this name includes cases of jaundice of varied etiology and pathogenesis. The early conception of the presence of cholangitis or duodenitis in every case has been disproved. When Bauer noted that excessive galactosuria occurred in so many of the patients with this type of jaundice he concluded that the essential defect was disease of the liver cells themselves. There are cases, however, in which the galactose tolerance test is negative, even when done early in the illness. It has been thought by Adler and Jeddeloh [81] that this variation in galactosuria indicates that there are two types of catarrhal jaundice, one due to liver cell damage and one due to actual catarrh of the bile ducts. Bockus and Tumen,[82] in a study of their cases of catarrhal jaundice, compared the patients with excessive galactose excretion with those in whom this was normal. They found that in the cases with positive response to the test, splenic and hepatic enlargement were more frequent and that the jaundice seemed to run a more prolonged course. The patients in whom the test was negative showed a higher incidence of biliary obstruction and catarrh. It was not felt "that the difference in the incidence of these findings was sufficient to warrant the conclusion that the galactose test in itself separates one type of so-called catarrhal jaundice from another." It does seem probable, though, that a positive galactose test in a case of catarrhal jaundice indicates that the icterus is due to actual disease of the liver cells themselves, that is, to hepatitis. When, on the other hand, the test is negative, especially early in the course of the illness, this fact suggests that the jaundice is due to obstruction in the ducts from inflammatory changes.

The results of our use of the galactose tolerance test in patients with icterus agree in general with those of Bauer and of Wörner. We have noted that in obstructive jaundice the test is practically always negative. On the other hand, positive results are obtained in those types of jaundice of which hepato-cellular damage is the cause. The majority of cases of toxic hepatitis and catarrhal jaundice show increased galactosuria. Negative re-

* Throughout this paper we have used the term catarrhal jaundice not because we feel that it represents a disease entity but because it is convenient to so designate a group of conditions at present not well differentiated.

sults to the test, however, may be obtained in undoubted cases of hepatocellular damage, even when this is of the utmost severity. In catarrhal jaundice a negative result to the galactose tolerance test may be obtained for one of two reasons. The test may have failed to show the presence of hepatitis or the jaundice may have resulted from obstructive biliary catarrh. This last possibility is particularly suggested by the occurrence of normal galactosuria in association with a spleen of normal size and evidence by duodenal drainage of biliary obstruction.

We feel that a positive galactose tolerance test in jaundice is almost pathognomonic of hepato-cellular damage. If the test is negative, this condition is not ruled out, particularly if the test is carried out late in the course of the illness.

We wish to express our gratitude to Dr. H. L. Bockus for kindly permitting us to use the records of many of his cases in preparing this paper.

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CONCERNING PLACENTAL HORMONES AND MENSTRUAL DISORDERS*

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CERTAIN placental extracts are now in common use in the treatment of disorders of menstruation. Following upon a not inconsiderable experience in 472 cases, it seems justifiable at this stage to discuss the theoretical basis for their use and also the results obtained by treatment. The first of these extracts is *Emmenin,* first defined by Collip (1930) as an alcohol-soluble, ether-insoluble extract of human placentae. In the light of recent work of Collip, Browne and Thomson (1932), it appears that Emmenin is probably a complex, containing as its active principle an ether-soluble trihydroxy-estrin, similar to the theelol of Thayer, Levin and Doisy (1931) and trihydroxy-estrin of Marrian (1930), but differing from them physiologically, as they in their turn differ from the theelin of Doisy (1929) or ketohydroxy-estrin of Butenandt (1929), in being relatively inert in the castrate animal, while preserving high activity in the immature animal with intact but prepubertal ovaries. Collip, Browne and Thomson (1932) therefore suggest that Emmenin is converted by the ovary, even the immature ovary, into some more active form of estrin, and this conception agrees well with clinical experience. It is interesting that Butenandt and Störmer (1932) find that their purest preparations of trihydroxy-estrin, free from all traces of ketohydroxy-estrin, have little activity in the castrate animal; their activity in the immature animal has not yet been reported.

The second of the preparations used is the anterior pituitary-like hormone extracted by Collip, Thomson, McPhail and Williamson (1930) from human placentae by means of acetone, and suitably purified. In contrast to Emmenin, it is insoluble in 85 per cent alcohol, and being destroyed by digestive enzymes, must be administered by injection. It is almost certainly identical with similarly purified extracts of human pregnancy urine, and the relation of these substances to the hormones of the anterior pituitary itself has been much clarified by the very recent work of Collip, Selye, Thomson and Williamson (1933). They have found that, while such anterior pituitary-like ("A.P.L.") extracts of placenta or pregnancy urine do act directly upon the ovaries, they can only partially prevent the regression caused by hypophysectomy; that is, the pituitary itself contains, as well as a substance acting upon the ovary in the same sense as does A.P.L., an additional or complementary substance, not present in placenta or pregnancy urine. On the other hand, there is definite evidence that A.P.L. has a stimulating action on the pituitary, probably indirectly, causing enlargement with signs of hyperactivity, and it is not unreasonable to suppose that

* Read before the American College of Physicians, Montreal, February 7, 1933.
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A.P.L. causes a release of the required complementary substance from the pituitary. In any case, the action of the A.P.L. in normal immature animals, as described by Collip, Thomson, McPhail and Williamson (1931), is to cause the ovaries precociously to assume normal adult size and structure, and to function, with the premature appearance of apparently normal estrus cycles; there is no action in castrated animals.

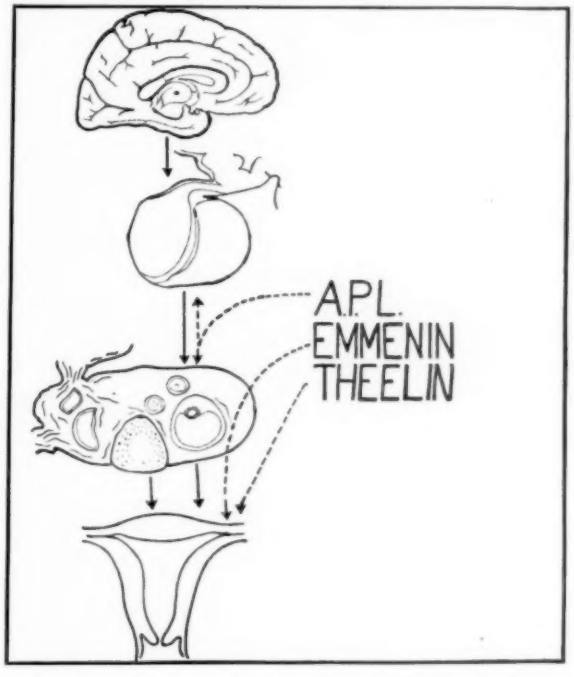

FIG. 1. Schematic illustration of the action of certain placental hormones.

Since there is some evidence of the presence of inhibitory substances in the pituitary (Collip) it is possible that alterations in this factor influence the function of the glands of internal secretion as revealed in ovarian dysfunction. Moreover, while certain centers in the hypothalamus undoubtedly influence the hypophysis, in order to clarify this most important point we must wait patiently for more experimental data.

These extracts have been employed in the treatment of disorders of menstruation of various kinds, but only in selected cases regarded as suitable for such treatment. Thus all cases in which pelvic lesions or abnormalities exist have been set aside, and are not further considered in this article. Moreover, it is known from animal experiments that disorders of the reproductive system may be due to the use of dietaries deficient in protein, in calcium, or in certain vitamins; and observations in Central Europe during the war justify the assumption that many present-day dietary fads and foibles contribute in a large measure to disorders of menstruation, particularly in

adolescence. In such cases, endocrine therapy, though not necessarily ineffective, does not appear to be entirely rational. The remaining cases may be clinically divided into those showing disorders of the menstrual flow, either in interval, duration or amplitude, and those showing disorders giving rise to pain, which in turn may be premenstrual, menstrual or intermenstrual.

Throughout this study the guiding principle has been kept in mind that menstruation is only the last, external manifestation of a long chain of physiological reactions. In considering the disorders of menstruation, it must be remembered that, while the macroscopic and microscopic structure of the uterus is in itself significant, this structure is under the control of the hormones of the ovary (estrin and the hormone or hormones of the corpus luteum). The formation of these hormones is in turn controlled by the internal secretions of the anterior pituitary which similarly regulates the thyroid and the adrenal cortex and in its turn is no doubt to some degree regulated by the brain and the sympathetic nervous system. These links, moreover, do not lead in one direction only. The hormones of the ovary do undoubtedly influence the activity of the anterior pituitary, and the rhythm of the menstrual cycle is not improbably due to an interaction between these two organs. Moreover, the effect of certain hormones of the ovary upon the anterior lobe of the pituitary gland may affect its influence upon other endocrine glands, and these may similarly affect the ovaries indirectly. That the higher links in the chain are not unaffected by events in the uterus is evident, for example, in the difference between pregnancy and pseudo-pregnancy in many animal species. Disordered menstruation, then, may be but the outward and visible sign of a dislocation of any one of these links; this idea is to be carried in mind in the subsequent discussion of the various disorders considered.

Amenorrhea

With the exception of instances of congenital obstruction in the Mullerian tract, there is a span in the life of the human female through which menstruation takes place with periodicity, interrupted normally by pregnancy and lactation. Apart from such physiological states, amenorrhea is dependent upon alteration of physiology in some link or links in the so-called endocrine chain, in which undoubtedly the pituitary is of paramount importance.

It has been found convenient to classify cases of amenorrhea in the following manner:

Primary Amenorrhea

(According to physical characteristics)

1. With prepubertal characteristics.
2. With normal post-pubertal characteristics.
3. With abnormal pre- or post-pubertal characteristics.
   (Endocrinopathies)

Secondary Amenorrhea

(According to menstrual histories)
1. Oligomenorrhea.
2. Oligomenorrhea with lapses.
3. Regular menstruation with lapses.

In the prepubertal type of primary amenorrhea, the stature may be within normal limits, but the secondary sexual characters are largely absent: axillary and pubic hair are developed at most to the degree of lanugo; the vaginal canal is small and frequently shows senile changes in the mucosa; the uterus is distinctly infantile. In such cases the ovaries, if they are developed at all, may be regarded as functionless; these individuals are physiologically or idiopathically prepubertal castrates. Absence of the sex element of the pituitary, without disturbance of the growth-promoting and other functions of that organ, would go far to explain such entities.

Somewhat similar in origin are the cases in which stature and sexual characters are normal, but in which menstruation has never occurred; the occasional occurrence of one or two periods of uterine bleeding simulating, but probably not exactly corresponding to, menstruation may be disregarded. Here again it is often tempting to suppose that the gonad-stimulating activity of the anterior pituitary has ceased; not, however, at so early a stage as in the preceding group, so that the secondary sexual characters have developed normally to a considerable degree. It is, on the whole, improbable that inflammation of the genitalia, or of the ovaries in particular, is an important cause of amenorrhea, since known cases of pelvic inflammatory disease rarely display amenorrhea in their subsequent course, and moreover it is certain that the amount of ovarian tissue normally present is greatly in excess of the amount required for the normal menstruation. For this and other reasons it seems more probable that the pituitary gland is primarily at fault. It is moreover quite unsafe to dismiss this possibility in cases where the sella turcica appears normal in the roentgen-ray; Cushing lends his authoritative support to the view that the gross size of the gland is no index of the degree of its activity.

The underlying cause of disturbed function is often obscure, but in many instances is traceable to some toxic condition or febrile state in childhood or adolescence frequently escaping the attention or memory of patient or parent; even in adult life the pituitary is susceptible to toxic influences including those of the puerperal state. The association of amenorrhea with tuberculosis is a time-honored observation, but in addition the disorder not infrequently follows scarlet fever, diphtheria or influenza; refractory amenorrhea and diabetes are frequently associated. Over 75 per cent of cases of amenorrhea are directly traceable to some of the conditions above mentioned.

First among the cases which show amenorrhea in the presence of abnormal postpubertal characteristics may be placed the cases of so-called Simmonds' disease, in which all the functions of the pituitary are depressed. As Calder has recently pointed out, the condition parallels that of the hypo-

physectomized animal. In such cases other aspects of the clinical picture overshadow the disorders of menstruation, which nevertheless may be one of the first signs of the insidious onset of the disease. From the point of view of the ovaries alone, the condition is doubtless very similar to that seen in the two preceding classes. We concur with Calder, who believes that cases of Simmonds' disease spontaneously arrested in some way before the typical clinical picture is established, are much more common than is generally supposed. In acromegaly, it may be assumed that there is a disturbance of balance between the several endocrine functions of the pituitary, whose effect upon the reproductive system is not yet clearly established. Cretinism may in some cases be due to pituitary dysfunction, in other cases the disturbed thyroid function may reflect upon the pituitary in such a way that the relations of the latter with the ovaries are deranged. Obesity and dystrophia adiposo-genitalis (Fröhlich Syndrome) are now generally attributed to a primary lesion in the hypothalamic region, which, however, influences the pituitary (and hence the ovaries and eventually the uterus) either passively or actively through nervous connections. The rôle which the adrenal cortex plays in cases of this class is as yet insufficiently explored.

The classification of *secondary amenorrhea* put forward above is not a purely academic one, but is based upon actual observation of the response to Emmenin treatment exhibited in the different groups. When there is a steady, progressive decline of flow—with lengthening of cycles, or leading eventually to a total lapse of menstrual discharge—the outlook for Emmenin therapy is bright, provided that the actual amenorrhea is not of long duration; the shorter the lapse, the more confidently may Emmenin be exhibited. If the amenorrhea has lasted 18 months or longer, Emmenin need not be expected to restore normal menstruation. Moreover, cases in which amenorrhea suddenly interrupts apparently regular menstrual cycles of normal amplitude of flow have been found to be very refractory to treatment, whereas in the two other types of secondary amenorrhea Emmenin, when effective, restores menstruation after an average of 23 days' treatment.

The prognosis is always problematical even in well selected cases, since at the onset of amenorrhea it is impossible to state whether such a disturbance is the result of a mild toxic influence on the pituitary gland, temporarily deranging its function, or whether the damage is more far-reaching, leading eventually to atrophy of the sex governing element of the hypophysis. The various types of *primary amenorrhea* do not respond to Emmenin, nor, it would seem, to any other form of endocrine therapy. Doubtless, if pituitary extracts were available which could reproduce the whole endocrine activity of the gland (as pituitary implants do in hypophysectomized rats) treatment might be undertaken with some prospect of success; but as yet no such extract appears to have been prepared even for laboratory purposes, much less for clinical use. Recent experimental findings by Collip and his collaborators indicate, however, that it is by no means necessary to despair of further progress in this direction.

Dysmenorrhea refers not merely to pain, but to a definite symptom complex, commonly involving nausea or other gastrointestinal symptoms and occasionally with signs of shock—the whole picture simulating an allergic phenomenon. The pain is typically premenstrual or at least occurs before the discharge has reached its greatest amplitude. It has long been held that

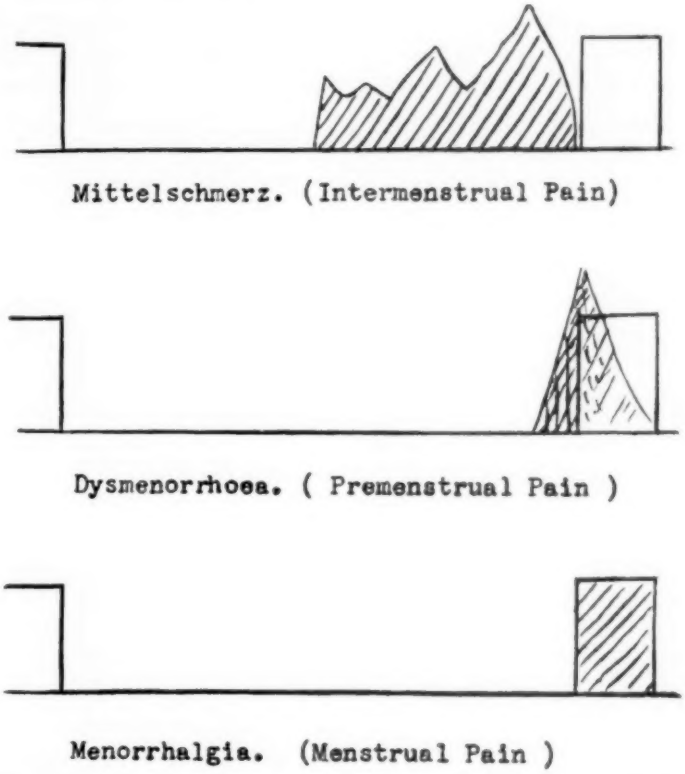

FIG. 2. Schematic indication of the relation of various types of pain to mentrual flow. (Hatched lines indicate pain; squares, menstrual epochs.)

the abnormal conformation of the uterus in such cases is responsible for this disorder. Against this view, however, may be urged the facts: (1) that the uterus is frequently normal; (2) that abnormal uteri may not be associated with dysmenorrhea; and (3) the less recognized fact that, whereas the uterus is more infantile (hence more likely to cause dysmenorrhea) at puberty than later, actually pain is only exceptionally complained of in the first few cycles (one in 40 cases) or even in the first three years of menstrual life. Beckwith Whitehouse associated dysmenorrhea with the subsequent passage of large flakes of endometrial tissue in the lochia, and found that not only was the endometrium in the progestational stage but that the strata compacta showed advanced decidua-like development; therefore he associated dysmenorrhea with the presence of a corpus luteum, either too active or too

long-lived, or both. This view is supported by Mazer's finding of an enlarged corpus luteum in a case with decidua-like progestational endometrium and by the fact regularly observed that the cycles in cases of dysmenorrhea are usually prolonged to 29 or 31 days. Beckwith Whitehouse suggested that treatment should be directed to curtailing this prolonged life of the corpus luteum, which in turn probably depends on some disturbance of the endocrine balance between ovary and pituitary. At the present time our knowledge of this balance does not suggest any means of readjusting it in the desired sense, but an alternative method of treatment does suggest itself. It is known from the animal experiments of Reynolds and Allen, and others, that estrin inhibits the action of corpus luteum hormones in inducing progestational changes in the endometrium. If these latter are responsible for dysmenorrhea, it is not illogical to attempt treatment by the administration of substances actually or (as in the case of Emmenin) virtually of the estrin type. In fact, the results of Emmenin treatment in such cases appear to go beyond expectation in this respect. The administration of Emmenin reduces the length of the cycles to 28 days, the uterus becoming less hard and increasing in size. Treatment should be carried through three cycles (since it is commonly found that every second cycle is less severe) and the dose then gradually reduced; only in a few cases should recurrences be anticipated. Failures should be reviewed in the light of a more searching history and investigation. Dysmenorrhea occurs commonly in patients of a definite physical type, rarely in the obese or plethoric; the typical case is ultrafeminine, active mentally and physically, weighing 95 to 115 pounds, and with slightly raised basal metabolic rate; the uterus is small, anteflexed and hard.

Pain occurring simultaneously with menstruation (menorrhalgia) is of a different nature. It occurs, as a rule, not in adolescence, but in adult life. There is usually, if not always, a lesion in the pelvic organs, real if not apparent; the cycles are frequently short and profuse; a large proportion of the cases are married, and sterility is an accompanying symptom. Intrauterine investigation will very frequently reveal the presence of a polyp or small mural fibroid, which not only stimulates the uterus to violent contractions but may cause regurgitation within the pelvic cavity through the Fallopian tubes, giving rise to intense peritoneal irritation. Endometriosis within the abdominal cavity gives rise to symptoms so similar that differentiation is exceedingly difficult; it is not impossible that this condition has existed undetected in some patients who have failed to respond to Emmenin.

Intermenstrual pain, or "Mittelschmerz," presents an almost unanswerable problem. It is characterized by the onset of sharp pain 12 to 14 days before the expected period, and the pain frequently continues with acute exacerbations until a few hours before the onset of the menstrual flow; the cycles are usually regular. The symptoms are so suggestive of chronic appendicitis that laparotomy is usually performed on these patients sooner or later; in spite of these exceptional opportunities for investigation almost

no convincing information bearing on the cause of the condition has been obtained. Unilateral oöphorectomy has frequently been performed, and it is found that thereafter pain does not recur on the operated side; this fact, together with the coincidence of the onset of pain with the alleged time of ovulation, suggests that the ovaries rather than the uterus are the seat of the pain. Yet since the pain is normally bilateral the relation to ovulation cannot be insisted on too heavily, though it is probable that even the ovary in which ovulation is not occurring at any one cycle shares with the other in certain disturbances such as hyperemia and congestion. Neither Emmenin nor A.P.L., nor, it would appear, any other form of endocrine therapy yet employed, has proved of any efficacy in this condition. Roentgen-rays have been employed by us in the treatment of intermenstrual pain. Following an artificial menopause of upwards of three months, menstrual epochs were unaccompanied by pain. The series is not large and sufficient time has not elapsed to speak with finality, yet our results seem to justify the consideration of such an heroic procedure in the treatment of " Mittelschmerz."

It should be emphasized that Emmenin therapy is essentially safe. In a group of 10 cases, Emmenin was administered daily (except during the periods) for several months without disturbing the normal menstrual cycles. If, however, administration was continued through the epoch, irregular prolongation of the flow or incomplete cessation was observed. No untoward effects, apart from occasional slight vertigo, headache, or nausea, in isolated cases were noted; three patients developed urticaria. No changes were observed in blood pressure levels; in some cases an initially high basal metabolic rate underwent slight reduction. The administration of Emmenin does not prevent impregnation nor interfere with gestation. Some 17 cases regarded as sterile became pregnant when treated for various menstrual disorders; the explanation is probably to be sought in the improved condition of the endometrium, or possibly in alteration of the vaginal reaction.

It may be of interest to review the possible cases of sterility attributable to the female, and the outlook for endocrine therapy in each type. Firstly, sterility may be due to failure of the ovaries to liberate viable ova; in some such cases, stimulation of the ovaries by anterior pituitary-like hormones might have a correcting influence; for example, in prevention of atresia of the follicle. Secondly, the ova liberated may fail to reach the uterus, whether because of some mechanical obstruction or because of derangement of the ciliary transporting mechanism; the latter type is that associated with endometriosis and ectopic pregnancies, and it is not inconceivable that it might be influenced by ovarian hormones. Thirdly, it is theoretically possible that the ovum and the sperm cannot unite to reproduce a viable embryo (for example, owing to association of lethal genes); such cases, if they exist, are doubtless refractory to all treatment. Fourthly, the uterus and vagina may be so abnormal—for example in the reaction of their secretions or the reactivity of their surfaces—that they are inhospitable either to the spermatozoa (so that intercourse could be fertile only at a very restricted period in

each cycle) or to the fertilized ovum (so that nidation fails or the embryo sooner or later loses its connection with the maternal tissues). Nearly all cases in this group could probably be influenced favorably by a correct supply of the hormones of the ovary, either introduced exogenously or evoked by stimulation of the ovary with appropriate extracts of the pituitary type.

It has already been indicated that the influence of the pituitary upon the ovaries is a reciprocal one; this is nowhere more evident than when ovarian function ceases, for example as a result of castration. Nevertheless, the origin of the various symptoms of the menopausal complex remains wholly obscure, and the treatment of the condition with placental hormones is a successful experiment without clear theoretical basis. The symptoms may include alteration in blood pressure and in metabolic rate, with irritability in addition to flashes (bouffées de chaleur) frequently appearing before the actual cessation of menstruation, that is to say, in the presence of some degree of ovarian function. They may persist long after apparent function has ceased. It is a striking fact that so-called "idiopathic" amenorrhea before the climacteric infrequently leads, as does castration at a similar age, to the production of menopausal symptoms. Emmenin has proved itself efficacious in the treatment of the menopausal syndrome of a milder form, provided that the symptoms have only recently appeared; the more general and more logical therapy is the A.P.L. extract, which has been employed with signal success in cases with intact ovaries.

The exhaustion of the potential follicles in such cases can be disproved histologically, but the fundamental alteration is possibly in the anterior pituitary gland. Further support of this thesis lies in the fact that with the administration of A.P.L. to such cases, the symptoms disappear in many instances, even if a considerable period has elapsed since the apparent termination of menstrual life, but since laboratory experiments and clinical trials have conclusively shown that the active principle employed is ineffective in the ovariectomized organism, the symptom complex of the so-called menopause is therefore apparently the result of deficient activity of both glands. This is further borne out by the fact that post-menopausal patients when treated with A.P.L. do not respond with menstruation, as do cases in mid-life with a corresponding period of amenorrhea. Moreover, the disturbance disappears even in certain cases with similar symptoms resulting from irradiation. These observations suggest that active graafian follicles and corpora lutea are not essential for the entire endocrine function of the ovary.

Possibly the most striking application of A.P.L. has been in the treatment of excessive uterine hemorrhage. A preliminary report on the effect of such treatment was presented by us before the British Medical Association, August 1930. A classification of the various types of this disorder has been already offered (Campbell, 1931); here again, as in the classification of secondary amenorrhea, the type encountered influences the outlook for therapy.

TABLE I

Varieties of Abnormal Uterine Hemorrhage

Group	Length of Cycle	Amplitude of Flow	Duration of Flow
A.	Normal	Excessive	Normal
B.	Normal	Excessive	Prolonged
C.	Normal	Excessive	Normal, superimposed on constant bleeding background
D.	Short (19–24)	Normal or excessive	Normal or prolonged
E.	Short (14 days)	Normal	Irregular
F.	Acyclic intermittent bleeding	Irregular	Irregular
G.	Continuous excessive hemorrhages	———	———

The last group (G) may be further subdivided into four categories, according to the mode of development of the continued bleeding which may arise.

(*a*) By confluence of regular cycles of varying length of interval, with unduly prolonged duration of the flow.
(*b*) By confluence of irregular periods of metrostaxis.
(*c*) Spontaneously, either after a normal menstrual cycle or more commonly after a period of amenorrhea.
(*d*) As an outcome of puberty.

The first five types (A–E) are grouped as menorrhagia, and distinguished from metrorrhagia, in which all sign of regular cycles has been lost; the hemorrhage is irregularly intermittent (type F) or continuous (type G). The metrorrhagia cases are further subdivided according to the history of the onset of the condition; especially, the cases in which metrorrhagia has arisen at puberty and continued steadily thereafter form a distinct subgroup. Too much stress cannot be laid on the need for careful exploration of the cavity of the uterus in all cases, in order to determine the character of the surface of the wall, as well as to obtain samples of endometrium for histological study. There is no cancer age.

It is considered that the primary defect lies in pituitary function and that the more or less typical picture in the ovary is a reflection of this altered function. The researches of Schroeder and of Shaw have associated metrorrhagia with the presence of an ovary containing no active corpora lutea but marked by large cystic follicles, a histological picture suggesting an excess of estrin formation over the formation of the luteal hormone or hormones. This idea finds confirmation in certain experimental studies of the effects of estrin administration. It would therefore seem that the aim of therapy should be either to supply luteal hormones or to cause the ovary to form them, the latter being at present the more feasible procedure. But whereas most of those workers who have striven to do this have used extracts which produce a pathological degree of luteinization in experimental animals, and which apparently—to judge by the case histories reported—have a similar

action in the treated patients, the object of A.P.L. treatment is to restore to the ovary a properly balanced structure and function. That this is not a vain hope is indicated firstly by the results of animal experiments, which show that, while A.P.L. stimulates the ovary, it does not produce excessive luteinization save in enormous doses, far in excess of those which can be employed clinically. Secondly, and more important, it should be noted that in the majority of the successful cases of whatever type, the end result is the reëstablishment of cycles normal in length and in duration and amplitude of flow. Only in the subgroup of metrorrhagias arising from puberty has a tendency for lapses of up to four menstrual cycles (possibly ascribable to excessive luteinization) made its appearance. On the other hand such cases may thus be presenting transient irregular menstrual cycles not infrequently observed in adolescence. A.P.L. has been used in a large number of cases of all types referred to earlier in the text; the response has been particularly gratifying.

While the true nature of *endometriosis* is not understood, there is reason to believe that deranged endocrine function permits the uterine mucosa to grow in a foreign locality. One patient with vaginal endometrial transplants was treated with A.P.L. The " rests " disappeared within six weeks. While such a result might have been fortuitous, it is considered worthy of reporting.

In nearly all of the cases in which success has been only partial or in which complete failure has been recorded, a more thorough examination has revealed the presence of some complicating factor obviously inaccessible to therapy of this type, such as the presence of an intra-uterine or adnexal lesion. Furthermore, it is essential that the ovaries contain potential follicles in order to correct so-called idiopathic uterine bleeding. It is therefore fitting to conclude with a repetition of the caution expressed at the beginning of this paper, that the first step in the introduction of endocrine treatment in any type of menstrual disorder is an accurate diagnosis, and the exclusion of cases in which structural abnormalities, neoplastic development or infective processes present an obstacle which no endocrine therapy can, or should be expected to overcome.

The extracts used in these studies were prepared in the Bio-Chemical Laboratory of McGill University by Prof. J. B. Collip. The method of preparation and physiological properties of these hormones have been published previously.

I wish to thank the staffs of the Royal Victoria Hospital and the Montreal General Hospital for their kind coöperation.

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THE EFFECT OF VITAMINS AND THE INORGANIC ELEMENTS ON GROWTH AND RESISTANCE TO DISEASE IN CHILDREN*

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During recent years more and more attention is being devoted by the medical profession to the rôle of minerals and vitamins in human nutrition. In the present paper we wish to direct your attention to some of the work being done in this field at the Hospital for Sick Children, Toronto. This work has been undertaken not with the object of discovering methods for the cure of various disease conditions, but in an attempt to determine the value and importance of these dietary factors for normal development and resistance against disease.

There are at least 10 inorganic elements which are absolutely essential for life, viz., sodium, potassium, calcium, magnesium, phosphorus, chlorine, sulfur, iodine, iron and copper. From the standpoint of the practising physician, we are fortunate in having to watch the supply of only three of these elements, because any reasonable diet will furnish the other seven elements in adequate amounts. The supply of the three elements, calcium, iron and iodine, however, should not be left to chance.

Although calcium is the fourth most widely distributed element in the earth's crust, its occurrence in foods is quite limited. Our two chief sources of calcium are milk and leafy vegetables. From the standpoint of the child's diet, it may be stated that it is absolutely impossible to furnish an adequate amount of calcium unless liberal amounts of milk are included in the diet. This can be readily demonstrated by the following. A diet comparable to that found in many uninformed families composed of rolled oats, bread and butter for breakfast; beef, potatoes, carrots, cabbage and rice for dinner; potatoes, bread and butter and honey or jam for supper, with four ounces of fluid milk to go on the rolled oats and rice, supplies only 0.3 gram of calcium. Yet the average ten year old child requires approximately one gram of calcium each day (Rose). The additional 0.7 gram of calcium required can be furnished by one pint of milk, or a total milk intake of 24 ounces per day. If all the milk is omitted the amount of calcium furnished by the remaining portion of the diet is reduced to the absurdly low figure of 0.17 gram. It is thus evident that we depend largely on milk to supply the large calcium needs of the growing child.

Iron is another mineral element that is not so widely distributed in food that its supply can be left to chance (Sherman). This is particularly true in

* Presented in part before the British Medical Association, London, England, July 1932. Read at the Montreal Meeting of the American College of Physicians, February 6, 1933.

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the case of the small infant, whose diet consists largely of milk and cereal, both of which foods are deficient in iron. Egg yolk, liver, spinach and other green vegetables are our richest sources of iron in foods.

From a series of experiments on rats we have found that with a lack of inorganic iron the rate of gain was reduced 33 per cent over a period of 11 weeks. The type of iron administered and also the presence of copper are essential in the diet, as proof of which a recent experiment was done in which a child with nutritional anemia was placed on a diet containing approximately 1.264 mg. of iron daily. The hemoglobin was 5.5 grams per 100 c.c. of blood. Copper sulfate was given for a period of three weeks in daily doses of 2 mg. No change was noted in the hemoglobin. For the next two weeks organic iron was added in the form of hemoglobin crystals, so that the child was receiving the equivalent of 12 grains of iron daily. Again the hemoglobin level remained the same. The organic iron was replaced by inorganic iron in the form of ferrous chloride in a dose of 33 mg. daily. The copper sulfate and the diet remained unchanged. In three weeks the hemoglobin had increased 2.4 grams per 100 c.c. of blood, and in another three weeks had reached the level of 11 grams of hemoglobin per 100 c.c. of blood, making a total increase of 5.5 grams of hemoglobin in six weeks. This demonstrates in the human what has been previously proved experimentally in the rat, namely, that copper, or copper and organic iron, are not efficient in hemoglobin regeneration.

With us, in the center of the North American continent, the iodine content of the water and the food is extremely low. We depend largely on iodized salt to furnish this element.

A lack of vitamin A in the diet results in a keratinization of the epithelial cells. Our chief supply of vitamin A is butter fat, egg yolk, carrots, spinach and cod-liver oil.

A lack of vitamin B_1 results in peripheral neuritis or beri-beri, while a lack of vitamin B_2 results in pellagra, and possibly certain skin diseases. Vitamins B_1 and B_2 are found largely in yeast, wheat germ, milk, liver, egg yolk, spinach and other leafy vegetables. Vitamin C, the anti-scorbutic vitamin, is found in oranges, lemons, tomatoes, cabbage and other fruits and vegetables. It is readily destroyed by heat in the presence of oxygen.

Vitamin D, the anti-rachitic vitamin, is not found in ordinary foods, with the exception of small amounts in egg yolk and summer milk. Fish oil, such as cod-liver oil, is our most concentrated natural source. In recent years vitamin D has been produced by the irradiation of ergosterol.

Vitamin E, the reproductive vitamin, is found in wheat germ, lettuce and other leafy foods.

In addition to the well recognized deficiency diseases produced by a lack of vitamins and minerals, we have studied the importance of these food elements to growth and resistance to infection. Each one of these vitamins and minerals is essential for life, so it is only reasonable to expect that if any one of them is omitted from the diet, the individual will eventually lose

weight and die. In animal experiments this has been found to be the case. In our rats fed a normal diet the average gain in weight over a period of six weeks was 100 grams. When calcium was reduced from the optimal figure of 0.612 per cent to 0.260 per cent, the average gain over the same period was 80 grams. In regard to phosphorus, we found that if this element was reduced from the optimal level of 0.450 per cent to 0.240 per cent, the animals, instead of making the normal gain of 100 grams in six weeks, gained only 66 grams. With a lack of iron, the rate of gain was reduced 33 per cent over a period of 11 weeks.

Some of the vitamins have been spoken of as the growth promoting vitamins, but a survey of figure 1 shows that a reduction of any one of the vitamins (with the exception of E) results in loss of weight.

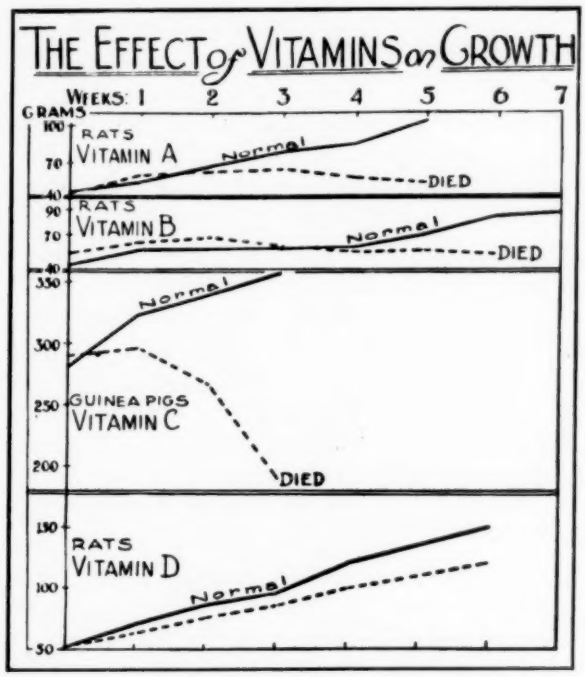

FIG. 1. The effect of a lack of any one of the vitamins on growth.

The influence of vitamin A in maintaining a normal condition of the epithelial cells of the respiratory tract and normal resistance against infection is so well recognized that this vitamin is frequently called the anti-infective vitamin. By a method devised in our laboratories by Dr. Elizabeth Chant Robertson, the effect of a lack of the vitamin B complex and of vitamin D has been studied. The procedure consisted of feeding the rat the desired deficient diet for a period of two to four weeks, and then giving by mouth a measured amount of an organism pathogenic for the rat, known as *Salmonella muriotitis*. The animals were then watched for a period of four

TABLE I

The Effect of the Vitamin B Complex on Resistance to Infection

Vitamin B Deficient Diet			Vitamin B Deficient Diet with 6% Dried Brewers' Yeast Added		
Total Number of Rats	Number of Survivors	Percentage of Survivors	Total Number of Rats	Number of Survivors	Percentage of Survivors
73	12	16%	68	47	69%

weeks, and the number of survivors noted. Blood cultures were made from the heart blood of all animals shortly after death, and the very occasional animal which did not show a positive culture was discarded as having died from some other cause. The results given in tables 1 and 2 show that a lack of the vitamin B complex and of vitamin D lowers the resistance of rats to infection.

TABLE II

The Effect of Vitamin D on Resistance to Infection

Rachitogenic Diet			Rachitogenic Diet with Addition of Vitamin D		
Total Number of Rats	Number of Survivors	Percentage of Survivors	Total Number of Rats	Number of Survivors	Percentage of Survivors
375	106	28%	364	201	55%

It has thus been shown that rachitic rats died in decidedly larger numbers after an oral infection with rat typhoid than similar controls fed vitamin D in addition to the rachitogenic diet. The following experiments were planned to test whether rachitic rats were also more susceptible to respiratory infections. As before, litters were divided, and half were put on a diet which caused rickets, and the other half were given the same diet with vitamin D (as 12½ per cent dried, vitamin D containing, bread) in addition. After 19 days on the diet the rats were all infected by six nasal instillations at daily intervals of a very heavy suspension of a pasteurella bacillus. Similar organisms cause pneumonia in rabbits, etc. Between the last two instillations a small amount of a dilute solution of brilliant green was dropped in the nose, as Bull had found that this increased the incidence of pneumonia.

All of the rats showed some nasal discharge after this treatment, but in the rachitic animals the discharge was more profuse and of longer duration. Three-quarters of the rachitic animals declined in weight after the infection, whereas all of the controls except one gained well. Seventy per cent of the rachitic rats died and showed evidences of pneumonia, and none of the controls with vitamin D died. All of the deaths occurred within six weeks after the animals were placed on the diet. The infecting organism was recovered from some of the dead animals, and from a microscopic examination of the pneumonic areas it appears that this organism causes a characteristic patho-

logical picture. The failure to recover the organism from all the dead animals was probably due to faulty technic which has now been improved.

The experiment is being repeated at present and the results to date are confirmatory.

The effect of the substitution of 17 per cent casein (the main protein in milk) for 17 per cent wheat gluten (a good cereal protein) on resistance to infection was tested. The diet was rickets-producing, and the calcium and phosphorus ratio was kept constant. The rats which received the casein containing diet grew on the average considerably better (40 per cent) than those fed the diet containing wheat gluten. Moreover, when their resistance to an oral infection with rat typhoid was compared after four weeks on the diets, there was a striking difference in favor of the casein, as in most of the experiments rats fed the wheat gluten died. One would be tempted to say that the greatly increased resistance of the casein fed rats was out of all proportion to the moderate increase in weight which the casein produced. Biochemists have convincingly shown that milk proteins greatly enhance the food value of cereals, and this work suggests that they also increase resistance to infection.

The effect of an iron deficiency in lowering resistance against infection in humans has been strikingly demonstrated by Dr. Helen Mackay.

Dental Caries

During the past 20 years numerous surveys have indicated that approximately 95 per cent of children suffer from this disease. At the present time there is probably no other disease to which the human body is subject that is so wide-spread or so fraught with potential danger to the health of the individual.

There is, of course, a marked diversity of opinion as to what is the cause of experimental caries, as a lack of various vitamins, an excess of vitamin D, a deficient supply of the minerals, calcium and phosphorus, and the consistency of the food have all been considered etiological factors in the development of this disease.

In 1927 Drs. Gordon and Mary Agnew of West China Union University in Chengtu, Szechwan, China, attempted the experimental production of caries in rats by feeding a diet low in vitamin D. After also making several thousand observations on the hill tribesmen of Eastern Tibet and the villagers of West China, they joined us in the Department of Paediatrics, University of Toronto, in 1930 in a rather extensive program. In approaching the problem of producing dental caries in animals by nutritional means, it was felt advisable to make as few variations in the diet as possible. It has been previously pointed out that there are at least 37 different elements necessary for normal nutrition. While a lack of any of these substances will interfere with the health of the animal as a whole, the close relationship between certain of these elements and definite pathological conditions is well recognized. For instance, the relation of iodine to the production of goiter,

of vitamin C to scurvy, of vitamin D to rickets, and iron and copper to anemia. It is not unreasonable, therefore, to consider that a limited number of these elements may be intimately connected with the normal nutrition of the tooth, and conversely that a lack of these elements may result in the development of certain disease conditions, including caries.

From the results of these many hundreds of gross and microscopical examinations of the rats' teeth, it was found that if vitamin D be present in the proper amount, but phosphorus be slightly deficient, the vitamin will prevent decay. If the phosphorus be very low, vitamin D may delay but cannot prevent the carious process. Sugar, so long blamed for caries, has been proved harmless in the rat, to which diets have been given containing as high as 62 per cent carbohydrate but including also adequate minerals and vitamins. The danger of excessive sweets in the diet, as far as dental decay is concerned, seems to be in the tendency for sweets to dull the appetite for the phosphorus containing foods, such as egg yolk, milk, meats, leafy vegetables and grains.

It is realized fully that the value of this work lies in its application to man. Accordingly, a total of approximately 350 children on diets containing varying amounts of calcium, phosphorus and vitamin D, have been observed during the past year in four institutions, with the aid of a group of dentists of Toronto. A most meticulous dental examination was carried out at the beginning of the investigation and will be repeated at its conclusion. During the period of the investigation the children have been divided into three groups as follows: (*a*) the control group, in which no change has been made in the diet; (*b*) a group who have been given additional vitamin D, and (*c*) a group who have been given both additional vitamin D and phosphorus. An interim examination has recently been made of the children in groups (*a*) and (*b*). To insure an unbiased interpretation of results, operators in examining the children were unaware of the groups into which the children were classified until all the records were completed. This examination showed in those children who had been given additional vitamin D a definite trend toward a lessened incidence of caries as compared to those who had eaten only the usual normal diet. Moreover, the children with added vitamin D showed that previously existing cavities had been largely arrested. In certain of these arrested cases a definite hardening of the cavity walls was apparent. The general tone of the gingivae and of the mucous membranes of the mouth of these children showed a definite improvement when compared with the gingivae and mucous membranes of those children who had not been given the additional supply of vitamin D.

From the observations on rats it may be concluded that for the first time true dental caries, indistinguishable from the human, has been produced experimentally, and that it may either be cured or prevented by adequate amounts of both vitamin D and phosphorus in the diet.

As already mentioned, vitamin D is not present in perceptible amounts in ordinary table foods, with the exception of small and variable amounts

in egg yolk and summer milk. Our tests show that eggs procured in the open market in Toronto in the month of March contained as little as two Steenbock vitamin D units per egg yolk. (One dram of standard cod-liver oil contains 46 Steenbock vitamin D units.) As physicians, we all know that we see extremely severe rickets in the winter months in infants receiving as much as one quart of milk per day. This makes it plainly evident that the human race does not depend on ordinary foods for its source of vitamin D. As shown in recent years, we depend on the ultra-violet rays of sunshine and skyshine to produce this vitamin in our bodies.

We have studied the variations in the anti-rachitic value of sunshine in Toronto over a period of some years, and found that the anti-rachitic potency of summer sunshine was approximately eight times as great as winter sunshine. The chief deciding factor in this change in potency is the altitude of the sun above the horizon. It was found that when the sun was below 35° it produced only a slight effect as compared to the effect produced when above 35°. In Toronto, even in the middle of the day, the sun is always below 35° for four months of the year; in the latitude of London this occurs for five months of the year, and in the latitude of Glasgow for six months of the year. This means that in Great Britain for five to six months of the year the sun has only a slight anti-rachitic effect.

This, combined with modern methods of living indoors, and the smoke pall over the large cities, makes it plainly evident that unless some special means are taken, the average individual will not receive an amount of vitamin D commensurate with optimal health.

The use of cod-liver oil and other vitamin D products obtained through the drug stores, has increased greatly in recent years, with a resultant improvement in the health of the rising generation. We have been accustomed, possibly, to think only of the anti-rachitic effect of vitamin D; the recent work of May Mellanby in Great Britain and McCollum in the United States has shown conclusively the value of vitamin D in the prevention of dental caries. It is inconceivable that a vitamin so essential for life in the early years should not be essential throughout childhood and adult life, although in a decreasing amount.

Taking all these facts into consideration, we felt that if an additional supply of vitamin D could be made available to the public which would be obtained by them at no additional cost, and by no effort on their part, we would be doing something well worth while. Accordingly, we incorporated vitamin D, in the form of irradiated ergosterol dissolved in corn oil, in the shortening used in making bread, so that each 24 ounce loaf contained the vitamin D equivalent of 3 drams of cod-liver oil. This bread is now being produced in some 15 cities in Canada and some 68 cities in the United States. (Figures 2 and 3.)

It has been stated that cereal grains furnish from 30 to 60 per cent of the calories of the average diet. Most cereal products as used today are highly refined and contain only a small amount of minerals, and are almost

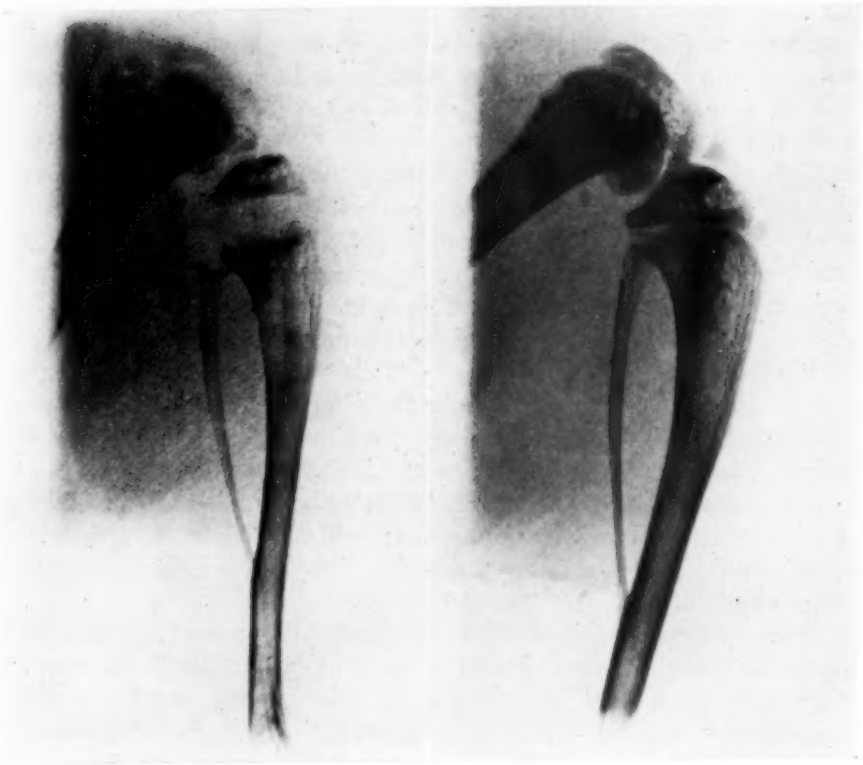

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FIG. 2. Roentgenogram of leg of rat fed on Steenbock's rickets-producing diet, containing 20 per cent of ordinary white bread. Blood phosphorus 2.0 mg. per 100 c.c.; percentage of ash in bones 30.1.

FIG. 3. Roentgenogram of leg of rat fed on Steenbock's rickets-producing diet, containing 20 per cent vitamin D bread. Blood phosphorus 4.6 mg. per 100 c.c.; percentage of ash in bones 49.5.

devoid of vitamins. This, combined with the rather extensive use of refined sugars, which are quite devoid of both minerals and vitamins, makes it evident that a very severe strain is placed on the remaining portion of the diet to furnish an adequate supply of both vitamins and minerals. In view of these facts, we felt that if an infant cereal, or breakfast cereal, could be devised which, in addition to supplying calories, would furnish minerals and vitamins in appreciable amounts, it should prove to be a valuable addition in the average dietary. However, on account of the general preference for refined and finely milled cereals, it was felt that in order to be generally used, the cereal should resemble these widely used products in taste, appearance, non-laxative effect and keeping qualities. Accordingly, a cereal has been devised that fulfills these requirements, and has the following composition: wheat meal (farina), 53%; oat meal, 18%; corn meal, 10%; wheat germ, 15%; bone meal, 2%; dried brewers' yeast, 1%; alfalfa, 1%. The wheat

germ is used on account of its high protein, mineral and vitamin content. It contains a moderate amount of vitamin A and is exceptionally rich in vitamins B_1 and B_2, and is the most concentrated known source of vitamin E. Dried brewers' yeast supplies vitamins B_1 and B_2, in addition to the amount already furnished by the wheat germ. Alfalfa is added on account of its high vitamin A and mineral content. We have found that one per cent of machine dried alfalfa furnished sufficient vitamin A for the cure of xerophthalmia in rats. The iron content of alfalfa is more than 130 mg. per hundred grams, which is 10 times the amount found in egg yolk, one of our most concentrated sources of iron in commonly used foods. The bone meal, which is an odorless, tasteless, white powder, is used on account of its high calcium and iron content. This cereal mixture has been used exclusively for the past two years in the Hospital for Sick Children, Toronto, and is also extensively used throughout the United States and Canada. In the infant wards, from the standpoint of a laxative, no difference was noted from the results obtained with the refined and finely milled cereals ordinarily used. The palatability of the product was evidenced by its being eaten with the same avidity as the ordinary cereal, not only by the infants, but also by the older children.

A study was made of the rate of growth of children fed daily two ounces, by dry weight, of this cereal mixture in place of ordinary cereals. Some 24 children in all were taken and divided into two groups, one group fed the ordinary cereals in a well-balanced diet, and the other group fed the special cereal mixture in the same well-balanced diet. The children were kept under identical conditions and weighed at weekly intervals over a period of 10 weeks. At the end of 10 weeks the groups were changed, and the ones on ordinary cereals now received the special cereal mixture and the ones on the special cereal mixture received ordinary cereals. Their weights were observed over an additional ten-week period. The results obtained are shown graphically in figure 4. It is to be noted that on the special cereal mixture the children gained four to five times their expected rate, in contrast with the average rate of gain obtained while on ordinary cereals.

We believe that more care should be given to insure an adequate supply of both minerals and vitamins in the diet. The importance of these food essentials in the maintenance of normal growth and resistance against infection is not as widely recognized as it should be. We, unfortunately, do not know the exact requirements of these food essentials. We also do not know the exact amounts furnished by many foods. We do know, however, that, due to the ease with which we can obtain purified carbohydrates, we are apt to suffer from insufficient amounts of minerals and vitamins, and, in occasional cases, of proteins. Nevertheless, we can go a long way towards overcoming the deficiencies so frequently encountered in the average diet if we build up our meals around five essential articles of food, namely, milk, to supply calcium and protein; meat, to supply protein; eggs, to supply

protein, vitamins and iron, and vegetables and fruit, to supply minerals and vitamins. The remaining calories required can be furnished readily by the refined cereal and sugar products.

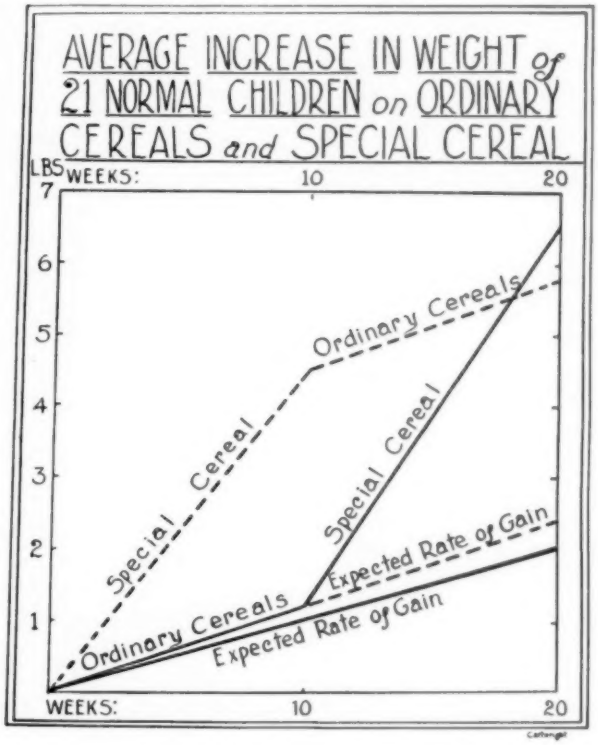

FIG. 4. Comparison of the increase in weight of children fed the special cereal and ordinary cereals.

After many years of practical experience, we are prepared to say that a more wide-spread observance of these few simple fundamental principles will go a long way towards improving the health of the community, and will materially assist us in reaching that goal which is the key-note of preventive medicine, namely, optimal health.

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FURTHER OBSERVATIONS ON THE TREATMENT OF PERNICIOUS ANEMIA WITH PARENTERAL HORSE LIVER EXTRACT*

INCLUDING ONE CASE OF PERNICIOUS ANEMIA FOLLOWING GASTRECTOMY

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Recently we[1] have reported that excellent remissions can be obtained in pernicious anemia patients with low blood counts from the subcutaneous or intravenous injections of a potent, highly purified horse liver extract. This communication entails a report of our observations on the further use of this injectable liver extract in 46 patients with pernicious anemia, covering a period of one year, during which time several thousand injections were given without local or systemic reaction. Although the oral administration of whole liver, liver extracts, and stomach substance are of unquestionable value in the treatment and maintenance of patients with pernicious anemia, the use of a potent injectable liver material in certain conditions is of decided advantage, and in many instances, a life-saving measure.

Cohn, Minot, and their associates,[2] as early as 1929, prepared a fraction from liver sufficiently pure to inject intravenously, which on administration produced maximal reticulocyte responses and a prompt increase in red blood cells. However, the large amount of material necessary to obtain this potent injectable liver fraction made it impractical from an economic standpoint for universal clinical use. Gansslen,[3] in 1930, was able to obtain good responses in the treatment of pernicious anemia patients from the daily intramuscular injection of an extract from five grams of liver. Castle and Taylor[4] reported maximal reticulocyte responses in two patients with pernicious anemia from a single intravenous injection of an extract prepared from 100 grams of liver. The unpleasant systemic reaction which occasionally followed the injection of this material, and the precautions necessary for its administration made it impractical and hazardous for general routine use. Later they[5] described a method of preparing an extract of liver suitable for intramuscular injection, and reported on three cases, showing a maximal reticulocyte response between the fifth and seventh days from the daily intramuscular injection of the extract derived from 10 grams of liver. Favorable responses in the use of various parenteral liver extracts have been reported by Aubertin,[6] Achard,[7] van Leeuwen,[8] Selander,[9] Harrington,[10] and others. Murphy[11] reported a series of 30 patients with pernicious anemia respond-

* Received for publication November 11, 1932.
This work was made possible by a grant from the Chappel Foundation for Organotherapeutic Research and was done at Northwestern University and Cook County Hospital. Technician, Miss Helen Legere.

ing favorably to parenteral cattle liver extract. The material used in the majority of the cases was of a high concentration, so that 5 cubic centimeters contained the active principle derived from 100 grams of liver. Although the use of such a high concentration undoubtedly alleviates the necessity of frequent or daily injections, they were frequently followed by a great deal of local discomfort and occasionally systemic reaction, characterized by anorexia, faintness, palpitation, and fever. Strauss and Castle[12] in their latest report obtained favorable results in a large series of patients from the use of the parenteral liver extract which they previously described[5] (2 cubic centimeters prepared from 10 grams of liver). In addition, they determined, from the treatment of 27 patients with varying single doses of parenteral cattle liver extract, that the amount necessary to produce a maximal reticulocyte response varies from the extract derived from 20 grams of liver to the amount derived from 100 grams.

Preparation of the Parenteral Equine Liver Extracts Used

The method of preparation which we previously described[1] was essentially similar to that of Strauss, Taylor, and Castle.[5] Absolute alcohol was added to the 70 per cent alcohol-soluble oral equine liver extract of known potency.[13] The resultant precipitate was dissolved in a convenient amount of water buffered with a phosphate mixture to make the solution isotonic and to adjust the pH of the finished product to 7.2. The solution was then filtered and 0.4 per cent tricresol was added as a preservative, and then standardized so that 1 cubic centimeter was equivalent to 10 grams of whole liver. Less than 400 milligrams of solid residue were present in the injectable extract prepared from 100 grams of liver.

We see no reason to believe that liver extracts made by different methods from equal amounts of liver will be equally potent. The present usage which seems to indicate the potency of a given preparation by a statement of the amount of liver used in its manufacture is misleading as pointed out previously by Meyer.[13]

Method of Administration of Equine Liver Extract and Summary of Patients Treated

This report was made possible through the courtesy and coöperation of the medical staff of the Cook County Hospital who turned over to us patients with pernicious anemia. Each patient under observation received a careful clinical, laboratory, and roentgenological examination. All patients, with the exception of two, presented the classical picture of pernicious anemia with achlorhydria. Free acid was found in the repeated gastric analysis of the two patients, although the clinical and hematological findings were typical of pernicious anemia.

The majority of patients treated remained institutionalized until the hemoglobin and the red blood cell count became normal. Complete blood

and reticulocyte determinations were made at five day intervals after the institution of maintenance treatment. Reticulocytes were counted daily during the period of expected response. Of the 46 patients receiving the injectable equine liver extract, 27 entered the hospital during a blood relapse, so that in the majority of patients a definite reticulocyte response could be determined. Twelve patients with comparatively normal hemoglobin and red blood cell counts, who had been previously treated with whole liver or oral liver extract, were referred to the clinic for maintenance treatment. Two patients with blood relapses were treated with an injectable equine liver extract prepared four months prior to its use. This was done to determine any variation in potency that might occur after aging.

Treatment with Intravenous Injections

Complete blood remissions were induced in three patients with pernicious anemia by the intravenous administration of the equine liver extract (table 1, cases 3, 6, and 11). From 2 to 4 cubic centimeters (1 cubic centimeter pre-

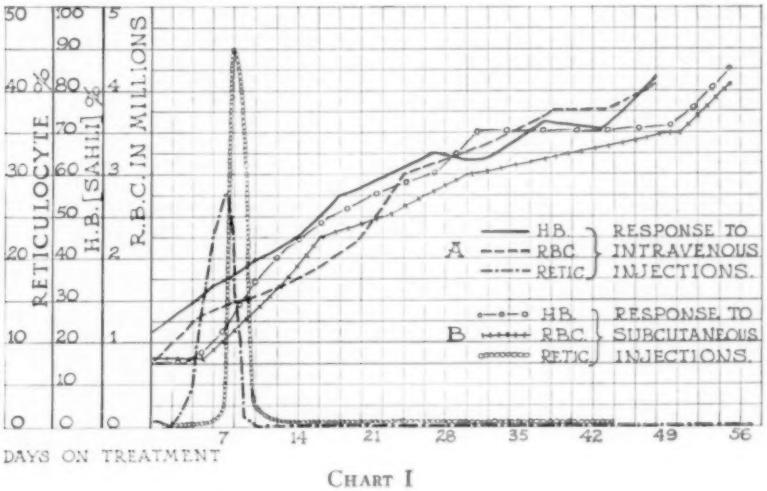

Chart I

pared from 10 grams of liver) of the material were injected at from one to three day intervals. Following the rapid injection of liver extract in the low-count patient, case 3, with an initial hemoglobin of 24 per cent and a red blood cell count of 840,000, a mild systemic reaction was occasionally noted. This consisted of an immediate drop in blood pressure, accompanied by a rapid, weak pulse, and dyspnea, and later followed by a generalized feeling of warmth. This systemic reaction was usually absent when the liver extract was injected slowly, i.e., less than 1 cubic centimeter per minute. No serious reactions were observed from a total of 60 intravenous injections. One of the three patients, previously resistant to treatment with large amounts of oral liver extract and whole liver (table 1, case 6), made a complete hematological remission in 57 days on intravenous injections of equine liver extract.

TABLE I

Primary Anemia

Responses of 22 Patients with Pernicious Anemia to Subcutaneous and Intravenous Injections of an Equine Liver Extract

No.	Sex	Age	No. of Relapses	Max. Reticulocyte %	Days on Treatment	Changes in Hemoglobin % (Sahli) Before	Changes in Hemoglobin % (Sahli) After	Changes in R.B.C. Millions Before	Changes in R.B.C. Millions After	Total Dosage	Average Dose and Injection Route	** C.N.S. Changes	Comments
††1	F.	51	1	25.2	58	25	80	.830	4.31	110 c.c.	2 c.c. Subc.	Mild	On maint. 92 days Req. 2½ c.c. q. 4.3 days
2	F.	46	1	21.8	70	22	80	.640	4.05	135 c.c.	2¼ c.c. Subc. (1 : 15)	Mod.	On whole liver for maintenance
†3	F.	60	2	27.6	48	24	83	.840	4.17	91 c.c.	3 c.c. Ven.	Mild	Rec'd total of 57 c.c. Ven. Cont'd daily subc. 2 c.c.***
4	F.	61	2	20.6	47	47	85	1.68	4.04	105 c.c.	2¼ c.c. Subc.	Adv.	On maint. 63 days Req. 2½ c.c. q. 4.3 days
5	F.	72	1	29.4	72	26	81	.890	4.14	128 c.c.	2 c.c. Subc.	Adv.	Sent to Psychopathic Hosp. Had marked mental changes
†6	F.	68	3	*5	57	41	81	1.08	4.14	73½ c.c.	2¾ c.c. Ven.	Mod.	Rec'd 3 to 4 c.c. Ven. at 2 to 4 day intervals***
7	F.	70	2	36.2	41	21	82	.780	4.05	82 c.c.	2¼ c.c. Subc.	Adv.	***
8	M.	49	1	16.8	72	14	77	.550	3.79	169 c.c.	2¼ c.c. Subc.	None	Still on treatment
9	F.	55	1	*13.6	50	39	83	1.42	4.11	102½ c.c.	1 c.c. to 2¼ c.c. Subc.	None	Also had hemiplegia***
10	M.	33	1	47.2	45	17	83	.750	4.15	100 c.c.	2 to 4 c.c. Subc.	None	On maint. 63 days Req. 2½ c.c. q. 2.5 days
†11	M.	29	2	*12.4	46	47	94	1.75	4.59	40 c.c.	2¼ to 4 c.c. Ven.	None	On maint. 85 days Req. 2½ c.c. q. 10.5 days
12	M.	52	2	*3	48	36	80	1.27	4.03	108 c.c.	2¼ c.c. Subc.	Adv.	***

TABLE I—*Continued*

13	M.	41	2	27.6	63	32	86	1.21	4.14	141 c.c.	2¼ c.c. Subc.	Mod.	On maint. 34 days Req. 2½ c.c. q. 2 days
14	F.	56	2	*	58	45	83	1.77	4.03	124 c.c.	2¼ c.c. Subc.	Adv.	Still in hosp. with C.N.S. changes. Daily inj. cont'd
15	M.	69	1	22.4	32	33	81	1.41	4.05	70 c.c.	2¼ c.c. Subc.	Adv.	On maint. 66 days Req. 2½ c.c. q. 3.7 days
16	F.	68	1	31.8	43	21	63	.910	3.06	130 c.c.	2 to 4¼ c.c. Subc.	Adv.	Left hosp. before treat. completed
17	F.	32	1	27.2	51	32	63	1.53	4.12	115 c.c.	2¼ c.c. Subc.	None	On maint. 90 days Req. 2½ c.c. q. 3.3 days
18	M.	45	1	34.6	40	23	62	.920	3.27	110 c.c.	2¼ to 5 c.c. Subc.	Adv.	Left hosp. before treat. completed
19	M.	32	1	22.6	53	21	82	1.10	4.08	142 c.c.	2¼ c.c. Subc.	None	2½ c.c. subc. inj. daily. Started on maint. treat.
20	M.	65	1	22.6	35	34	65	1.13	3.02	79 c.c.	2¼ c.c. Subc.	Mod.	***
21	M.	57	2	27.6	69	18	71	.610	3.50	139 c.c.	2¼ c.c. Subc.	None	Still on treat. 2½ c.c. daily subc. inj.
22	M.	73	1	*	45	58	84	2.44	4.13	112 c.c.	2½ c.c. Subc.	Mod.	This treat. preceded by oral frozen liver ext. 1 oz. t. i. d. On maint. 46 days. Req. 2½ c.c. q. 3.1 days
TOTAL				441.2	1042	676	1719	25.510	85.39	2222			
AVERAGE PATIENT				27.6	47	30.7	78.1	1.159	3.881	101			
AVERAGE GAIN						47.4		2.722					
AVERAGE DAILY GAIN (Per Patient)						1.0% Hb. (Sahli)			57,914 R.B.C.		Aver. Daily Dose 2.14 c.c.		

* Cases in which our treatment was preceded for several days by other treatments which have absorbed maximal reticulocyte peak. ** In this column, none, mild, moderate, and advanced denote the degree of central nervous system changes present, if any, prior to treatment. *** Did not return for maintenance treatment. † Responses obtained from intravenous injections. †† Also had bleeding cervical polyp removed while on liver treatment.

Cases 2, 16, and 19 received a more concentrated and purified equine liver extract during the period of reticulocyte response (1 c.c. prepared from 15 grams of liver).

Case Report

A markedly anemic-appearing white woman entered the hospital on June 14, 1929, in a semi-stuporous condition. The blood examination on entrance revealed a hemoglobin of 50 per cent and a red blood cell count of 1,100,000 and the characteristic blood findings of pernicious anemia. A complete remission was induced by the liver diet, and the patient was sent home on July 18, 1929, with a normal hemoglobin and red blood cell count. Two years later, June 10, 1931, she reëntered the hospital complaining of nausea, vomiting, weakness, and numbness and tingling of the hands and feet. The patient stated that after leaving the hospital, she followed the liver diet haphazardly up to eight weeks before, when she developed an upper respiratory infection manifested by fever, chills, chest pains, cough, and expectoration, which was followed by the symptoms for which she reëntered the hospital. The blood examination now revealed a hemoglobin of 73 per cent and a red blood cell count of 3,200,000. She was started on a standard accepted cattle liver extract, receiving the amount equivalent to 720 grams of whole liver. Although her symptoms subsided, she made comparatively little hematological progress while on treatment for 26 days, and was discharged on July 7th with a hemoglobin of 78 per cent and a red blood cell count of 3,360,000. Three months later, November 4, 1931, the patient reëntered the hospital for the third time, with a complete blood relapse. The hemoglobin was 29 per cent and the red blood cell count 890,000. Three and one-half cubic centimeters of equine liver extract were injected intravenously at from one to three day intervals for a total of 23 injections. A complete hematological remission was produced in 57 days, the patient leaving the hospital on December 12, 1931, with a hemoglobin of 81 per cent and a red blood cell count of 4,140,000.

Treatment with Subcutaneous Injections of Horse Liver Extract

Equally as good responses were obtained from subcutaneous injections of this liver extract as when it was injected intravenously. The ease of administration and its harmless and bland nature when injected subcutaneously were decided advantages, making it ideal for routine therapy. About 3000 injections of equine liver extract have been given subcutaneously, and in no instance did a systemic reaction occur. No apparent local reaction was noted in the majority of patients. Occasionally a local erythema and a feeling of warmth followed the injection, and in the exceptional patient some local pain persisted for several hours. Because of these negligible reactions, patients on maintenance doses continued their treatment by self-medication, returning to the clinic at from two to six week intervals for a hematological check-up.

Twenty-four patients with relapses were treated with daily injections of subcutaneous liver extract. The average dose used was 2.5 cubic centimeters, containing the active principle of 25 grams of horse liver. Patients entering the hospital in a semi-comatose or moribund condition received two or three injections (50 to 75 grams) daily until evidence of a reticulocyte response was obtained, and then once daily until the hemoglobin and red blood cell counts became normal. These results are tabulated in table 1. The maximal reticulocyte response was obtained between the fifth and seventh days and varied in this series of cases from 16.8 per cent to 47.2 per cent. The average of the entire group was 27.6 per cent, omitting the pa-

tients who received previous therapy, which had absorbed the maximal reticulocyte peak. With the occurrence of a remission the usual signs of clinical improvement were noted. This was evidenced by the subsidence of gastrointestinal symptoms, followed by an increase in appetite, strength, and weight, and a gradual recovery of the patients' general condition to a state of normality.

TABLE II

Differential Findings from Blood of Pernicious Anemia Patients in Chart I before and after Treatment with Equine Liver Extract
(Case numbers correspond to case numbers in Table I)

Case	Ex. **	Arneth Index* (% in 100 cells counted) 1	2	3	4	5	6	Total No. of Lobes	Differential Count (% in 100 cells counted) N.	E.	B.	L.	M.	(N.R.C.)
1	B	0	4	33	49	13	1	374	47	0	0	51	2	
	A	2	4	36	42	13	3	369	42	4	0	47	7	
2	B	0	1	20	50	22	8	420	52	0	0	44	4	
	A	1	7	39	44	8	1	354	62	2	1	30	5	
3	B	0	1	11	44	31	13	444	72	0	0	22	6	4
	A	1	4	46	45	3	1	348	55	4	0	39	2	
4	B	0	2	28	44	21	5	399	50	0	0	48	2	3
	A	0	9	43	36	11	1	352	57	2	0	35	6	
5	B	0	8	42	47	7	1	371	64	2	0	30	4	
	A	1	2	37	46	14	0	370	60	2	0	35	3	
6	B	0	4	19	51	29	2	426	38	0	0	60	2	1
	A	0	6	49	39	6	0	345	58	4	0	33	5	
7	B	0	0	24	44	25	7	415	63	0	0	35	2	1
	A	0	18	39	36	6	1	333	74	3	0	15	7	
8	B	0	6	35	37	18	4	379	53	4	0	40	2	
	A	0	6	52	35	6	1	344	49	6	1	38	6	
9	B	1	4	25	44	23	3	384	58	0	0	39	3	
	A	0	5	33	47	12	3	375	45	0	0	52	3	
10	B	0	4	19	43	25	8	410	73	1	0	26	0	
	A	0	7	41	34	18	0	363	66	2	1	30	1	
11	B	0	4	52	32	12	0	352	41	0	0	56	3	
	A	0	7	53	35	4	1	336	52	4	0	40	4	
12	B	0	2	29	40	20	9	395	39	2	1	54	5	1
	A	0	11	44	34	11	0	345	59	2	0	30	9	
13	B	0	3	22	40	28	7	414	83	0	0	16	1	
	A	0	2	32	45	18	3	388	80	3	0	11	6	
14	B	0	2	31	44	18	5	393	41	2	0	54	3	
	A	0	4	52	32	12	0	352	77	0	0	20	3	
15	B	0	9	40	36	9	6	363	65	2	0	29	4	
	A	0	13	37	40	10	0	347	45	10	1	40	4	
16	B	0	1	21	40	30	8	423	56	2	0	40	2	1
	A	1	6	25	45	20	3	386	56	4	1	33	6	
17	B	0	4	33	37	20	6	390	41	0	0	57	3	2
	A	3	15	61	17	3	1	293	51	2	0	42	5	
18	B	0	3	35	37	17	8	392	58	0	0	39	3	
	A	0	7	46	38	7	2	351	80	0	0	19	1	
20	B	0	3	28	35	24	10	410	50	0	0	48	2	2
	A	1	7	41	37	10	4	362	66	5	0	23	6	
21	B	1	8	38	37	14	3	367	85	0	0	15	0	
	A	2	12	45	29	10	2	339	65	0	0	32	3	

* Neutrophillic granular cells classified according to number of nuclear lobes. The hemoglobin and red and white cell determinations are recorded in Table I. ** In this column "B" denotes before treatment; "A" denotes after treatment with equine liver extract. In the Differential Count columns, N denotes Neutrophils; E—Eosinophils; B—Basophils; L—Lymphocytes; M—Monocytes; N.R.C.—Nucleated red cells.

Differential examination of the white cells prior to treatment of each patient showed a marked shift of Arneth's index to the right. The average number of nuclear lobes in 100 cells counted from a series of 20 patients was 391.5. (Table 2.) During the period of the maximal reticulocyte response, when evidence of blood regeneration was most marked, a definite tendency for the nuclear index to shift toward normal was noted. This temporary reaction was due primarily to the immature cells, released from the stimulated and hyperactive bone-marrow, occurring at the onset of a remission. Following the end of the reticulocyte response, a gradual shift of Arneth's index to the right was again noted, the average number of nuclear lobes in 100 cells counted at the end of treatment being 352.6. This finding was persistent in the majority of patients even after a normal hemoglobin and red blood cell count was obtained, and, from our experience, indicated that only a temporary remission is obtained from liver therapy, and that maintenance treatment is necessary to prevent another relapse.

A complete hematological remission was produced in four to eight week intervals, the majority of the patients treated showing an average daily gain of 1 per cent hemoglobin (Sahli) and 57,914 red blood cells from the average daily injection of 2.14 cubic centimeters of equine liver extracts.

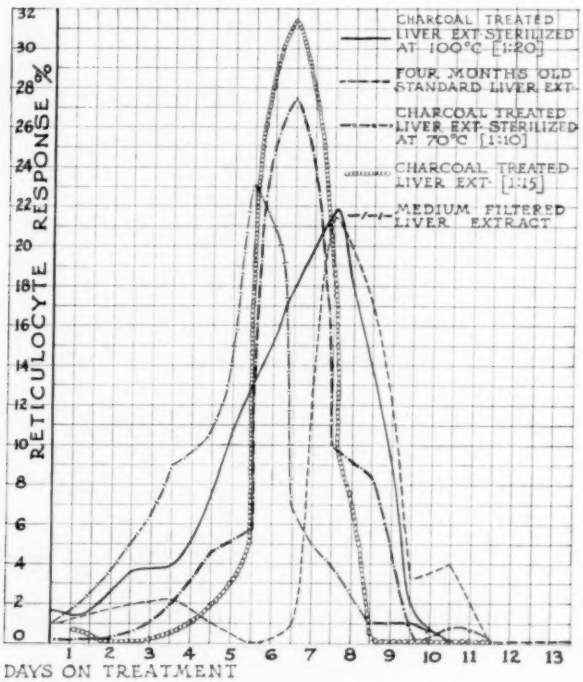
RETICULOCYTE RESPONSE %
DAYS ON TREATMENT
CHARCOAL TREATED LIVER EXT. STERILIZED AT 100°C [1:20]
FOUR MONTHS OLD STANDARD LIVER EXT.
CHARCOAL TREATED LIVER EXT. STERILIZED AT 70°C [1:10]
CHARCOAL TREATED LIVER EXT. [1:5]
MEDIUM FILTERED LIVER EXTRACT

CHART II

Reticulocyte Responses to "Old" and Specially Treated Injectable Equine Liver Extracts *

In order to determine the potency of the standard equine liver extract after aging, two patients with pernicious anemia received daily injections of a four-month-old preparation. The responses observed in both cases were similar to those obtained from the freshly-prepared equine liver extract. The reticulocyte response of one patient is listed in chart 2.

Studies were also made on the effect of the standard extract, which had been treated by various methods in an attempt at further purification. Four such special preparations were used; the first was filtered through activated cocoanut charcoal and sterilized in ampoules at 100° C.; the second was similarly treated with charcoal and subjected to fractional sterilization at 70° C.; the third was filtered through hardened paper, S & S; and the fourth was ultra-filtered through a medium collodium membrane. In none of these special preparations was there any definite reduction in the percentage of solid residue. All produced prompt reticulocyte responses when injected subcutaneously into patients with pernicious anemia. (Chart 2.) It is apparent that aging, treatment with charcoal, sterilization by heat, and ultra-filtration through collodium membranes, do not affect the potency of the active anti-pernicious principle.

Responses of Seven Cases of Pernicious Anemia, with Unusual Complications, to Subcutaneous Injections of Equine Liver Extract

This group included patients with pernicious anemia complicated by other diseases, which in several instances were of primary etiological importance and perhaps indirectly responsible for the anemia.

Case I

A white female, 40 years of age, entered the hospital on December 16, 1931. From the history on record, the patient had previously entered the hospital four and one-half years before, during a blood relapse. At that time, in addition to the usual findings of pernicious anemia, a four plus spinal and blood Wassermann was obtained. The patient was given anti-luetic treatment, plus the liver diet. A complete remission was obtained; she was discharged from the hospital and advised to continue further anti-luetic treatment at a dispensary. For several years she conscientiously followed the anti-anemia diet. In addition, she received numerous courses of anti-luetic treatment, consisting of neoarsphenamine, bismuth, mercury, and iodides. The patient stated that for nine months prior to her present hospital entrance she had neglected to eat liver. After abandoning the liver diet, she began to feel weak and tired. This was followed by noticeable pallor, and loss of appetite and weight. The weakness became progressively worse, so that she was finally confined to bed. On admission to the hospital, the blood examination revealed a hemoglobin of 27 per cent and a red blood cell count of 780,000. Blood Wassermann and Kahn tests were negative. Treatment was started with daily subcutaneous injections of equine liver extract, and a complete remission was again produced in 77 days.

* Since this paper was submitted, batches of equine liver extract, aged one year, still showed evidence of retained potency.

TABLE III

Responses of Seven Cases of Pernicious Anemia with Unusual Complications to Subcutaneous Injections of Equine Liver Extract

Case	Sex	Age	No. of Relapses	Max. Reticulocyte %	Days on Treatment	Changes in Hemoglobin % (Sahli) Before	Changes in Hemoglobin % (Sahli) After	Changes in R.B.C. in Millions Before	Changes in R.B.C. in Millions After	Total Dosage	Average Dose and Injection Route	Complications
1	F	40	2	7.8*	77	27	81	.870	4.06	138 c.c.	2 c.c. Subc.	Syphilis.
2	M	59	1	*	26	65	80	2.96	4.17	54 c.c.	2 c.c. Subc.	Septic arthritis.
3	M	53	1	7.4*	75	40	75	1.19	3.09	201 c.c.	2¼ c.c. Subc.	Ileo-cecal tuberculosis with ileo-colostomy.
4	F	68	2	12.2	57	34	63	1.56	2.70	124 c.c.	2¼ c.c. Subc.	Pyelonephritis and bronchopneumonia.
5	M	63	1	27.4	144	17	54	.710	3.49	333 c.c.	2¼ c.c. Subc.	Tuberculous bronchopneumonia.
6	M	55	1	*	30	44	58	2.77	4.25	60 c.c.	2 c.c. Subc.	Gastric syphilis: subtotal gastrectomy.
7	M	62	2	**	6	69	64	2.43	2.40	12 c.c.	2 c.c. Subc.	Cancer of stomach with peritoneal and liver metastases.

* In each case our treatment was preceded by other treatment, which had absorbed peak of reticulocyte response. ** No reticulocyte response because of initial high hemoglobin and red blood cell count.

Case II

A white male, 59 years of age, entered the hospital on January 4, 1932, complaining of epigastric distress, frequent attacks of diarrhea, weakness, loss of appetite, and numbness and tingling of the hands and feet. On entrance, the blood examination revealed a hemoglobin of 35 per cent and a red blood cell count of 1,540,000. Treatment was started with equine oral liver extract, the patient receiving the extract equivalent to 720 grams of whole liver daily. A good hematological response was obtained. After the hemoglobin had risen to 65 per cent and the red blood cell count to 2,960,000, this treatment was replaced by daily injections of equine liver extract. Shortly after, while walking about, the patient injured his right knee. This was followed by swelling, redness, tenderness, and pain. Several days later the swelling became progressively worse and was associated with severe pain, tenderness, and a high temperature, with evidence of fluctuation over the knee joint. The knee joint was incised, and a large amount of pus was evacuated. The joint was drained for several weeks. A complete hematological recovery was obtained in 68 days on the combined treatment, and the patient was sent home on March 12, 1932, with a normal hemoglobin and red blood cell count.

Case III

On April 6, 1932, a white male, 53 years of age, entered the hospital, complaining of weakness, abdominal cramps, diarrhea, and numbness and tingling of the hands and feet. The blood examination revealed a hemoglobin of 40 per cent and a red blood cell count of 1,190,000. The history obtained from the patient was that he had had frequent attacks of diarrhea for the past 15 years. Twelve years before he was seized by an attack of nausea, vomiting, and pain in the abdomen, which was diagnosed as an intestinal obstruction. An operation was performed, and on opening the abdomen a mass was found in the ileo-cecal region, which was diagnosed as tuberculous, and an ileo-colostomy was performed. Following the operation, the patient made a very slow recovery, remaining bedridden for three months, and at no time since did he regain his normal strength or weight. However, in spite of the persistent weakness and the continuous diarrhea, he was able to get around fairly comfortably for six years. He was then again seized with a similar attack of abdominal pain and fecal vomiting, which necessitated a second operation. Although he obtained relief from his obstructive symptoms, he was practically bedridden for a year, and required morphine and opiates for the relief of abdominal distress and diarrhea. At this time he was also severely anemic, for which he received injections of iron. Following this he was again able to be up and around, but the weakness and pallor persisted and became progressively worse, so that two years later he was admitted to a state institution. At that time his hemoglobin was 23 per cent and his red blood cell count 1,200,000. A diagnosis of pernicious anemia was made, and he was started on whole liver and liver extract by mouth. He was discharged from the hospital 12 weeks later with a hemoglobin of 70 per cent and a red blood cell count of 3,800,000, having also gained 22 pounds in weight. After leaving the hospital he felt fairly well, but he was unable to continue the liver diet and after six months reentered the hospital with similar complaints. He was then transferred to another state institution, where he was confined for one and one-half years, during which time he definitely improved and felt fairly comfortable. He was again discharged and sent home on September 1, 1931. The patient failed to follow the liver diet at home, and had a gradual recurrence of symptoms, which became progressively worse, necessitating hospitalization. He entered our service on April 26, 1932. In addition to the characteristic blood findings of pernicious anemia previously described, a gastric analysis after an Ewald meal showed a free acidity of 38° and a total of 58°. The

blood Wassermann was negative. The gastrointestinal roentgen-rays showed no organic lesion in the cecum, although a definite fixation, suggestive of adhesions, of the cecum and ascending colon was noted. The patient received daily injections of subcutaneous equine liver extract. A reticulocyte response of only 7.4 was obtained on the eleventh day. However, a comparatively good hematological response later followed in spite of the persistent gastrointestinal disturbances, consisting of frequent attacks of abdominal pain and diarrhea. At the end of 73 days of equine liver extract therapy, the hemoglobin was 75 per cent and the red blood cell count 3,080,000.

Case IV

A white female, 68 years of age, entered the hospital on February 24, 1932. From the history obtained, she had felt fairly well until a year before, when she began complaining of pain and numbness and tingling of the hands, and became unable to hold or grasp objects with security. Shortly afterwards, these symptoms were followed by weakness and dyspnea. Several weeks before admission she noticed swelling of the feet, and a sensation of bloating and epigastric distress. On entrance, the blood examination revealed a hemoglobin of 34 per cent and a red blood cell count of 1,560,000. The systolic blood pressure was 210 millimeters of mercury and the diastolic pressure 90. The blood Wassermann was negative. The icteric index was 16. Treatment was started with daily subcutaneous injections of equine liver extract. A reticulocyte response of 12.2 per cent occurred on the ninth day. Although a good hematological response was obtained after several weeks of treatment, the patient became semi-stuporous, gradually entered into uremic coma, and died 52 days after entrance to the hospital, with a hemoglobin of 63 per cent and a red blood cell count of 2,070,000.

Case V

A markedly emaciated male, 63 years of age, entered the hospital in a semi-stuporous condition on December 21, 1931. The only history obtainable was that 16 years before the patient had been treated for pulmonary tuberculosis in a sanatorium and discharged as an arrested case. After this illness he had felt perfectly well until several months before admission, when he began complaining of weakness, epigastric distress, and attacks of nausea and vomiting. The blood examination on entrance revealed a hemoglobin of 22 per cent and a red blood cell count of 720,000. The blood findings were characteristic of primary anemia. The temperature was moderately high, ranging between 100° and 103.5° F. There was a persistent hacking cough, at times followed by the expectoration of mucopurulent sputum. After careful clinical and roentgenological examination, a diagnosis of tuberculous bronchopneumonia was made.

The patient received two injections of subcutaneous equine liver extract daily, equivalent to 50 grams of whole liver. In spite of the septic temperature, a reticulocyte response of 27.4 per cent was obtained on the sixth day. Although the bronchopneumonic process subsided, the patient still continued to follow the clinical course of an active pulmonary tuberculosis. During six months' stay in the hospital he received subcutaneous injections of equine liver extract twice daily. Because of the positive sputum, he was transferred to the tuberculosis hospital. The hemoglobin was then 53 per cent and the red blood cell count 3,340,000. Several days later he rapidly sank into a coma and died.

Case VI

A severely anemic white male, 55 years of age, entered the hospital on October 7, 1931. The patient stated that on April 12, 1928, he had had a gastric resection per-

formed at the Research and Educational Hospitals. The summary of the clinical and laboratory findings present at that time were obtained from a report, published in 1929, by Dr. H. Singer,[14] his attending physician. The patient had then complained of abdominal pain and vomiting, which had been present for the preceding three years. For a few weeks before admission emesis had occurred five to six times daily, so that he had finally become unable to retain liquid foods. There had been marked loss of weight and extreme weakness. The gastric analysis after an Ewald meal showed an absence of free acid and a combined acidity of only five degrees. The hemoglobin was 68 per cent and the erythrocyte count was 4,100,000. The blood Wassermann and Kahn tests were four plus. The roentgen-ray examination with an opaque meal showed an obstructive lesion with an hour-glass constriction and canalization in the middle of the stomach, and marked gastric stasis. A possibility of gastric syphilis was strongly considered, and mercury and iodides were administered for several days. Because of lack of improvement in the symptoms of obstruction, a laparotomy was performed. A markedly thickened and shrunken stomach with an hour-glass constriction in its distal portion was found. An extensive resection was performed, leaving only the proximal 5 centimeters of the stomach. From the gross and microscopic examination of the resected portion, a diagnosis of gastric syphilis was made. Following the operation the patient made an uneventful recovery and was discharged from the hospital on April 21, 1928.

The history obtained regarding his present illness was that for two and one-half years after the operation he had remained comparatively well, his only complaint being a feeling of epigastric fullness after meals. He then, however, began to complain of weakness, palpitation, dyspnea, and numbness and tingling of the hands and feet. In the two months preceding his admission he had been unable to walk up two or three flights of stairs without becoming completely exhausted. Several days prior to his hospital entrance he had a mild attack of diarrhea. The blood examination on admission was characteristic of pernicious anemia, showing a hemoglobin of 22 per cent and a red blood cell count of 1,120,000. The blood Wassermann was four plus. The gastric analysis after an Ewald meal showed an absence of free and total acidity. There were definite objective sensory disturbances of both lower extremities. The patient was started on equine oral liver extract, receiving one ounce three times daily, which was equivalent to 720 grams of whole liver. An unusually slow increase in hemoglobin and red blood cells was obtained, so that at the end of 60 days on treatment his hemoglobin was 44 per cent and his erythrocyte count was 2,770,000. The oral liver extract was discontinued, and daily injections of subcutaneous equine liver extract were started. At the end of 30 days on this treatment a normal red blood cell count was obtained (4,250,000) with a hemoglobin of 58 per cent.

Case VII

A white male, 62 years of age, entered the hospital on July 10, 1931. The patient stated that a year before he had begun to have pain in the epigastrium. The pain was described as dull in character. It radiated across the upper part of the abdomen; it usually occurred during or immediately after meals. This pain was occasionally associated with anorexia and vomiting. About two months before admission he began to suffer from weakness, dyspnea, and a numbness and tingling of the hands and feet. The blood examination on entrance revealed a hemoglobin of 16 per cent and a red blood cell count of 629,000, with other characteristic findings of pernicious anemia. He was placed on oral liver extract. He improved rapidly, and at the end of 72 days he was discharged from the hospital with a hemoglobin of 76 per cent and an erythrocyte count of 3,120,000. At this time no gastrointestinal examination was made. On July 12, 1932, he reëntered the hospital, complaining

chiefly of severe epigastric pain, anorexia, and vomiting, occurring immediately after the intake of food. In the preceding six months he had lost 60 pounds in weight. He had noticed that occasionally he passed tarry stools. On entrance his hemoglobin was 69 per cent and the erythrocyte count was 2,430,000. Stomach analysis after an Ewald meal showed gross evidence of blood and an absence of free acid. Roentgen-ray examination revealed a mass involving the pars media of the stomach with retention. A diagnosis of carcinoma of the stomach was made. An exploratory operation was done on July 21, 1932, and a carcinoma was found involving the entire stomach from the cardiac to the pyloric end with metastasis to the liver and peritoneum.

It is apparent from the study of Cases 6 and 7 that the removal or destruction of the stomach wall was probably directly responsible for the subsequent anemia. Castle and his co-workers[15] have definitely demonstrated that an activating substance essentially necessary for hematopoiesis and present in normal gastric secretion is absent in the gastric secretion of patients with pernicious anemia.

Maintenance Treatment

The most difficult problem in the treatment of patients with pernicious anemia in a large institutional practice is maintenance. The majority of patients previously treated with the liver diet have at some time or other returned to the hospital in another relapse. This was usually due to neglect of their instructions to eat the necessary amount of liver, or to their inability to obtain the liver or an equivalent amount of liver extract. Occasional permanent remissions from liver therapy have been reported. The patients under our observation required continuous therapy to maintain their blood at a normal level. Twenty-six patients continued maintenance treatment with the injectable equine liver extract by self-medication, returning to the clinic at three week intervals for a hemoglobin and erythrocyte determination. During a period covering eight months of observation, the average dose required was two injections of equine liver extract a week. Our preliminary results indicate that the frequent injection of a potent anti-pernicious-anemia principle is more advantageous in maintaining a normal blood level and preventing complications than single large injections given every two or three weeks.

Response of Neurological Complications

A subsidence of nervous symptoms was usually noted in patients with blood relapses following the institution of treatment with the injectable equine liver extract. In many instances a definite improvement of the mental and spinal cord symptoms was observed. Patients with subacute combined degeneration of the spinal cord showed definite subjective signs of improvement. Daily subcutaneous injections were continued in patients with cerebro-spinal symptoms even after the hemoglobin and red blood cell

count became normal. Because of the short duration of the period of observation of cases on this treatment, definite conclusions as to objective neurological improvement cannot be drawn at this time. A more detailed report will be made later, in association with Dr. Gonda, the attending neurologist, who has collaborated with us in this aspect of the treatment of patients with pernicious anemia.

Advantages of Subcutaneous Equine Liver Extract Therapy

The use of a potent and injectable material is of particular advantage in the treatment of the following types of cases: Patients with an aversion to liver; those who are vomiting, or are unable to assimilate orally administered preparations because of gastrointestinal dysfunction; stuporous or comatose patients; and uncoöperative patients.

Conclusions

Forty-six patients with pernicious anemia treated with subcutaneous injections of equine liver extract were studied.

Twenty-two patients entering the hospital during a blood relapse, and treated with the parenteral equine liver extract made a prompt hematological and clinical recovery.

Favorable responses were obtained in five patients receiving special equine liver extract, showing that aging, sterilization at 100° C., and ultrafiltration did not affect the active anti-pernicious-anemia principle.

Seven patients with unusual complications, including one case of pernicious anemia following gastrectomy, treated with parenteral equine liver extracts, are discussed.

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RESEARCH IN ELECTROCARDIOGRAPHY*

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A modified apparatus[1] and technic[2] for obtaining electrocardiograms was reported in 1932. This paper reports the further development of the apparatus and its use in electrocardiographic research.

The Need for Better Apparatus

The introduction of the string galvanometer by Einthoven in 1903 marked a great advance in the methods of recording rapid changes of small electric currents. In most electrical engineering applications, however, the string galvanometer has been largely displaced by the oscillograph. The latter instrument although by no means as sensitive as the string galvanometer is of a more sturdy design and can be adapted to give larger scale records with greater accuracy than can readily be obtained from a string galvanometer.

Because the oscillograph is a less sensitive instrument, some form of amplifier must be used in conjunction with it because the electrical energy produced by heart action is not sufficient to operate an oscillograph vibrator element directly. The factors which must be considered in designing such an amplifier have been discussed[1] previously.

Three major considerations prompted the development of this apparatus. The first of these was that although the quantity which concerns us in electrocardiographic studies is the potential difference produced during the heart beat, the quantity which a string galvanometer actually responds to is the current caused by that potential difference flowing in the vibrating string. These two quantities although related are not necessarily directly proportional to each other. Unless exact proportionality does exist, however, the string galvanometer deflection cannot possibly be proportional to the potential difference which causes it. This lack of proportionality (or nonlinearity, as it is usually called) may come about because the measuring circuit includes not only the substantially constant resistance of the galvanometer string but also the resistance of the body and contacts which may or may not be constant. Furthermore these two resistances are of about the same size and the current through the string is therefore controlled just as much by the body and contact resistance as by the substantially constant resistance of the string.

The fact that the body resistance varies from one person to another, and sometimes from one lead to another on the same person, leads to a procedure

* Read at the Montreal Meeting of the American College of Physicians, February 10, 1933.

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in the use of the string galvanometer which in view of the second difficulty to be discussed is not at all satisfactory. In order to "standardize," it is frequently necessary to change the tension of the string. It is a well known fact that as the tension of a vibrating string is changed the natural frequency of vibration of the string changes also. The effect of changing the tension from one patient to another is therefore to alter the relative response of the string to current variations of different rates of change.

In describing current variations of the periodic type (such as are encountered in electrocardiography) it is customary to speak of the different harmonics or frequency components of the variation. It is well known that in speech and music we deal with sound waves which are of a very complex nature but which can be thought of as composed of a number of simpler oscillations which are harmonically related to each other, i.e., the frequencies are all simple integer multiples of the lowest or fundamental frequency. In a similar way the periodic wave which we get on an electrocardiographic record can be broken down mathematically (by a process known as harmonic analysis) into a number of simple sinusoidal oscillations which have frequencies related harmonically to the fundamental frequency. In the case of the electrocardiogram the fundamental frequency is the number of times per second the heart beats, say, about 1.25 cycles per second.

After we know by such a harmonic analysis the highest frequency component which is present to an appreciable degree in electrocardiograms, the range of frequencies to which a measuring instrument must respond is completely defined. Using the apparatus designed in this research, a typical normal * electrocardiogram was obtained and was then broken down by harmonic analysis, with the results shown in table 1.

TABLE I

Harmonic	Relative amplitude
Fundamental	1.00
2	2.36
20	3.24
30	0.75
35	1.27
40	2.27
45	1.33
50	0.94

It will be noted, for example, that the amplitude of the fortieth harmonic is more than twice as great as that of the fundamental. If the fundamental frequency is 1.25, then the frequency of the fortieth harmonic is $40 \times 1.25 = 50$ cycles per second. To carry this analysis still further an approximate pencil and paper analysis was carried out and it was found for example that the 100th harmonic (125 cycles per second) was about twice as large as the fundamental.

These findings indicate clearly that the shape of the electrocardiographic

* A conservative case was chosen. Many abnormal records contain high harmonics to a greater extent than was found here.

wave cannot be reproduced accurately by any instrument which fails to respond to these higher frequencies. In figure 1 is shown the results of a test made on a standard type of string galvanometer operating with normal tension on the string, as compared with the amplifier and oscillograph used in

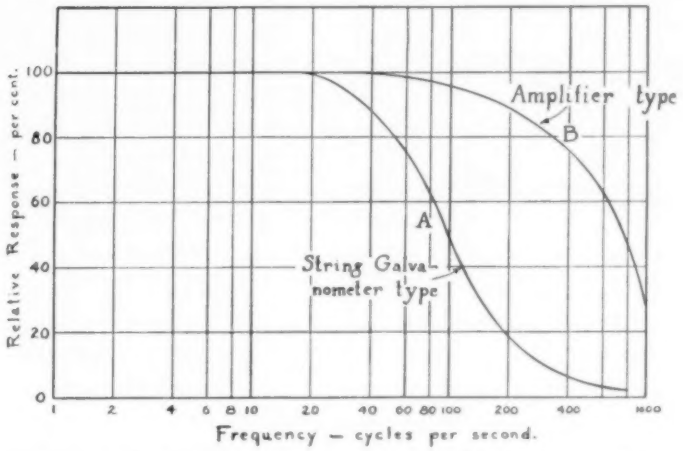

FIG. 1. Comparison of the frequency response of a standard type of string galvanometer with that of the new amplifier type of electrocardiograph.

this work. It will be observed that the response of both instruments falls off at the higher frequencies * but that the string galvanometer falls off much more rapidly than the other. If we are willing to tolerate as much as 15 per cent decrease in response, the string galvanometer used cannot be considered satisfactory for recording variations in which harmonics of 50 cycles or higher appear, while on the same basis the amplifier-oscillograph combination can be considered satisfactory up to 250 cycles, which is the 200th harmonic of the fundamental. This failure to respond to the important high frequencies is the second and by far the more important major difficulty encountered with the string galvanometer.

The objection has been raised that it is not necessary to use an amplifier and oscillograph in order to overcome this difficulty but that it is only necessary to increase the tension of the galvanometer string. While it is true that if the tension is increased the *relative* response of the string galvanometer will be improved at the higher frequencies, the absolute response or sensitivity will be decreased. If we are willing to tolerate a much smaller amplitude of record than is at present obtained, the frequency response of the string galvanometer can be materially improved, but of course the accuracy in the measurement of the smaller record will be less than at present.

The results of harmonic analysis shown above have been found to disagree with similar analyses made by other workers. One writer [3] states that components beyond the fourth harmonic are of no importance, and our atten-

* The response of the amplifier oscillograph instrument has recently been considerably improved over that shown in the above figure.

tion has been called on various occasions to the lack of agreement between the results reported above and those formerly obtained. The explanation of this disagreement lies in the fact that the conflicting harmonic analyses were made on records produced by string galvanometers and not on records produced by instruments capable of passing high frequencies to an adequate extent. Obviously if the recording instrument in making its record does not respond to higher frequencies, mathematical analysis cannot make these frequencies appear in the record. The fact that there is a disagreement between the analyses made on these two types of records provides strong secondary evidence that the string galvanometer as *customarily used in electrocardiography* is not capable of responding to all the essential frequencies. To one well acquainted with harmonic analysis it is quite evident that the large rates of change of potential which appear in correctly reproduced electrocardiograms must be thought of as being produced by high frequency harmonic components, and if the recording instrument fails to respond to these high frequencies the final result cannot be a true picture of the phenomenon measured.

The third important consideration which led to the development of this apparatus was the small size of the electrocardiogram as usually obtained. If these curves are to be used for qualitative analysis only, there is no real need for a large size record. But if, as is actually the case, we are attempting to make a quantitative study of the records and base our conclusions on the numerical results, then it is obviously desirable to obtain a record which is large enough to permit accurate measurements without being so large as to be unwieldy and obscure. In the present work both the voltage scale and the time scale have been enlarged approximately by the same ratio. It is possible also to increase the time scale to the point where a single heart beat is recorded on a 36-inch record but this is considered a freak speed.

The record is traced with a narrow, sharply focused line rather than with the broad line so commonly seen on string galvanometer records.

The Apparatus Used

The original form of the apparatus has previously been described.[1] It consists principally of a specially constructed vacuum tube amplifier and a standard type of oscillograph * using one supersensitive element for reproducing the electrocardiogram and a standard element for putting on the time wave.

* The bifilar oscillograph was chosen principally because it is readily available, relatively inexpensive, rugged, and easily maintained. Some workers have used oscillographs with a moving iron vane or needle. These must be carefully designed with respect to the magnetic properties of the iron, and the iron itself must be specially selected in order to obtain a linear response curve and also to avoid difficulty from hysteresis (if hysteresis is present to any appreciable extent, the deflections for *increasing* current will not be the same as those for *decreasing* current). The cathode-ray oscillograph offers great possibilities for experiment, but it is still very much in the developmental stage and is not as yet sufficiently reliable and trouble-proof to be used by the average technician.

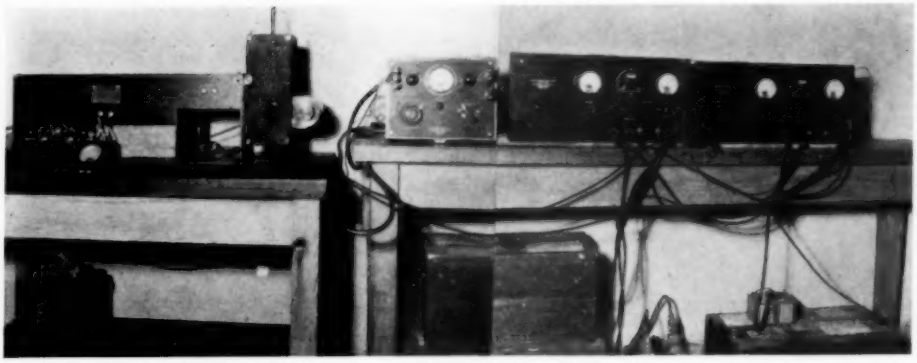

FIG. 2. New apparatus. Left to right: oscillograph, control box, amplifier A, and amplifier B. Batteries under the table.

Recently a new apparatus (see figure 2) along the same lines has been built in which two amplifiers are used together with an oscillograph containing two supersensitive vibrators for recording the electrocardiograms and a single standard vibrator for the timing wave. A suitable switching and calibrating circuit is incorporated through which connections to the patient are made. In using this apparatus the records are made in pairs; the actual procedure is to record Leads I and II and then Leads I and III. By this arrangement it is possible to obtain the exact time relations between the voltages in the leads without recording all three leads simultaneously. The record is made on an inexpensive recording paper five inches in width; a camera was specially designed to carry a 25-yard roll of the paper and is arranged so that a single record can be cut off and developed without removing the camera from the oscillograph.

Space does not permit an adequate discussion of the amplifier as used but it should be emphasized that great care is required to build a successful high-gain amplifier for electrocardiographic applications. This is particularly true because the operation of the amplifier is to be recorded by an oscillograph and small variations which if present in a radio amplifier would be practically inaudible, are quite visible and disturbing if they appear on an oscillograph record.

By using an amplifier it is possible to eliminate almost completely the first difficulty discussed in the previous section, that is, the presence of body resistance in the measuring circuit. Instead of connecting the body in series with a resistance of comparable magnitude as in the string galvanometer method, the amplifier input circuit is designed so that it has a resistance about 100 times as large (250,000 ohms) as the average body resistance. Hence if the body resistance varied all the way from zero to its maximum value it could make no more than a small percentage change in the final result, and it is obvious that the ordinary variations which occur will have a negligible effect on the final record.

Suggested New Technic

It has become evident that the greater amplification and speed made available by this apparatus make visible details of the electrocardiogram which are inconspicuous or which cannot be seen in records taken by the standard technic. A few examples to show this are given (figures 3 and 6). Although it is possible to drive the camera with a speed at which a single

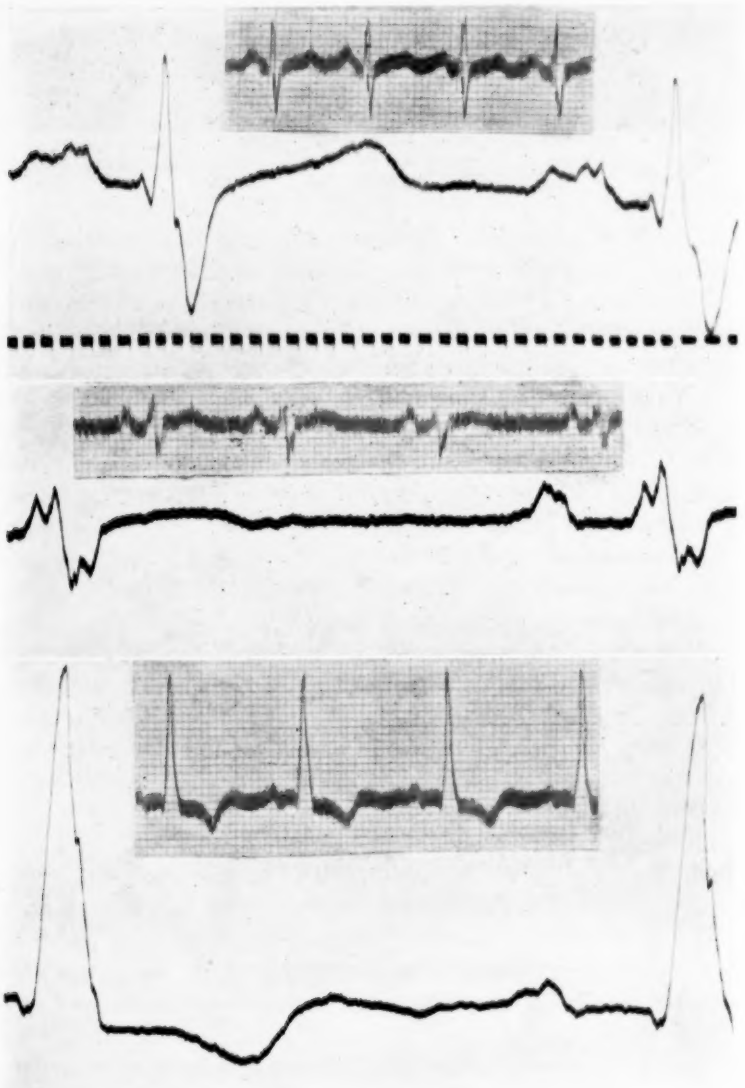

Fig. 3. Short strips of three different electrocardiograms, with a section of the string galvanometer record from the same patient superimposed on each. The time record is shown only in the upper tracing. Note greater details and speed suggested as suitable in the new records.

heart beat is recorded on a 36-inch strip of paper, we have reached the opinion by study of numerous records that a more conservative speed is preferable. Figure 4 is included to show some of the variations in speed and the fact that the second notch in the P-wave is not visible until the record is spread out by using the higher speed.

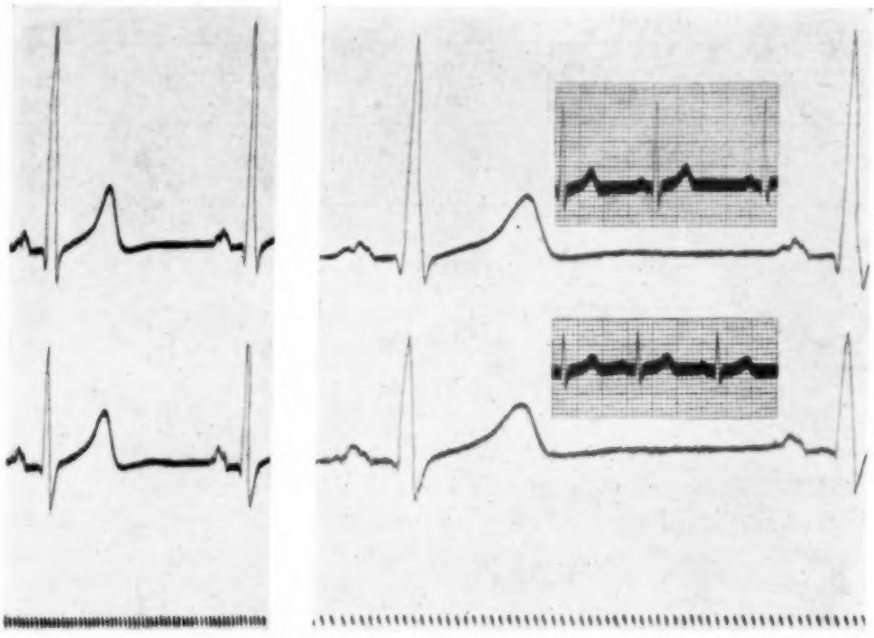

FIG. 4. *Left:* Lead II above, Lead I below, taken simultaneously. Time record at bottom. *Right:* Same at greater speed, and with corresponding string galvanometer records superimposed. Note appearance of the second notching of the P-wave in the faster record of Lead II. Reduced by one-third.

The amplification is limited by the width of the photographic paper (five inches), that is, by the requirement that the largest wave recorded be inscribed on the paper. The ability to amplify the waves, without loss of accuracy in contour, appears to be of much assistance in disclosing their full details, especially in those instances in which the waves would otherwise be small. For example, see the accompanying illustrations.

It is suggested, therefore, that a technic be adopted that amplifies and spreads out the electrocardiogram so that all pertinent details may be studied and accurately measured.

NEW PROBLEMS

An analysis of the voltage recorded, or the amount of excursion from the baseline was made [2] on records taken from a series of 25 patients with the string galvanometer and with the new apparatus. The results are given in table 2.

TABLE II

Comparison of Voltage Recorded by the New Apparatus with That Recorded by an Einthoven String Galvanometer in a Series of 25 Patients

Wave	Status *	Number of leads †	Average difference ‡	Maximal difference ‡
P	same	19		
	lower	15	0.02	0.07
	higher	41	0.04	0.18
Q	same	37		
	lower	12	0.02	0.06
	higher	26	0.03	0.13
R	same	3		
	lower	24	0.09	0.34
	higher	48	0.19	0.90
S	same	34		
	lower	31	0.09	0.34
	higher	10	0.04	0.11
T	same	23		
	lower	12	0.03	0.05
	higher	40	0.03	0.15

* As compared with same wave recorded by string galvanometer.
† Standard three leads for each patient, so number of leads equals 75.
‡ In millivolts.

Table 2 shows a difference in the voltage recorded in a large majority of the leads and in all waves; it was not constant in direction. The maximal difference found was 0.9 millivolt greater in an R-wave. This analysis shows clearly the large differences which can occur in recording and interpreting the same variation by the two methods. It is also noted that the differences in voltage we found were greater in frequency and in amount than those reported by Ernstene and Levine [4] in their comparison of a series of similar size between the string galvanometer and a commercial electrocardiograph using an amplifier and moving-ion oscillograph.

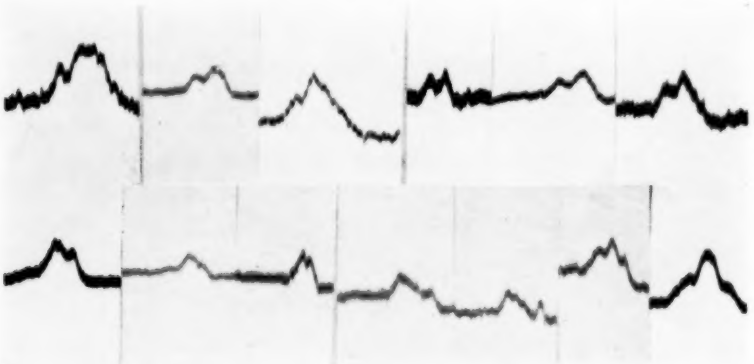

FIG. 5. Series of P-waves. Upper row shows a single notch with the second peak the higher. Lower row shows the left-hand five P-waves also with a single notch but the initial peak the higher. The last two P-waves are indented twice and the middle peak is the highest of the three components.

The study of the details made visible by the new records is continuing. In figure 5 are shown a series of P-waves; they appear to be classifiable in groups according to the number of components made by the notches in them. In the upper row are six of these P-waves indented by a single notch and with the greater amplitude in the second component. In the lower row this condition is reversed in the first five examples, i.e., the waves are indented by a single notch but the first component, or peak, is higher. The last two of the lower row show three components with the middle one the highest.

Figure 6 contains examples of Q–R–S complexes showing the clarity

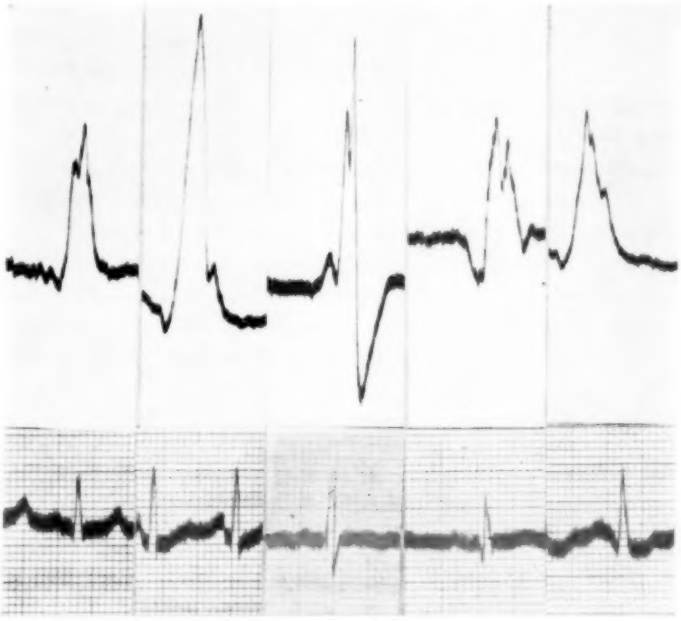

FIG. 6. Series of Q–R–S complexes above with their corresponding string galvanometer records below each. Note absence of the small S-wave recorded in the two galvanometer records at left end of the series.

with which their various contours can be visualized. It is noted that the first two lack the small S-wave recorded in the string galvanometer record from the same two patients below. Examination of the standardization photographed on the string galvanometer record in these cases discloses a little overshooting which may reasonably account for the appearance of the S-wave on the record. In spite of considerable care in the technic of taking electrocardiograms with the string galvanometer we have been unable to avoid this defect in some of the records taken with this instrument. Since becoming engaged with the work pertaining to the new instrument we have become increasingly conscious of this difficulty in constantly obtaining records free from overshooting when using the string galvanometer.

It is hoped that we may obtain a large number of records with the new

instrument taken on patients with coronary thrombosis in order to determine what new details, if any, may be disclosed in the progressive changes in the S–T interval and T-waves.

It is of course impossible as yet to determine what significance may be placed upon these newly disclosed details of the electrocardiograms. The matter must wait for the correlation of a sufficient number of clinical and necropsy findings and, perhaps, some experimental work on animals. There is hope that new information of value may result, and it appears obvious that the only way to get the possible new light regarding the heart lies in continuance of the use of the new instrument.

From time to time various observers have reported the use of needle electrodes in the taking of electrocardiograms. We have persistently failed to obtain satisfactory records with the use of needle electrodes with the string galvanometer. The difficulty appears to be that when using needle electrodes we cannot obtain a satisfactory standardization; whenever we seek the deflection of 1 cm. for one millivolt imposed on the string the tension of the latter must be loosened so much that the string shadow tends to move off the field. This trouble which is presumably due to excessive polarization, has been so constant that we feel doubt as to the accuracy of the technic employed in records obtained with the use of needle electrodes and so believe these electrocardiograms to be distorted. As might be expected we found no difficulty in taking electrocardiograms with needle electrodes when using the new instrument. Such records are then the same as those taken with ordinary electrodes.

An application of the new apparatus has been made to physiologic research. Dr. F. H. Pratt has recorded the beats of the lymph hearts of frogs. This has been done both with the lymph hearts in their normal position and with one of them after transplantation to the base of the tongue, where it resumed its rhythmic beating after the lapse of a few days although it no longer was propelling lymph. The beat of the transplanted lymph heart was found to more closely simulate that obtained directly from the ventricle of the frog's blood heart, than it did that of the lymph heart in its normal position and with its normal connections with the spinal cord. This work becomes more impressive when it is pointed out that the size of the lymph hearts in the frog varies from but one to two millimeters in diameter.

It may be of interest to add that these lymph hearts are possessed by all amphibia and reptiles. They assist in the forward propulsion of the lymph. In the case of the frog they occur in two pairs, the anterior located under the scapulae and the posterior just lateral to the vertebral column at the caudal end of the body. They beat at an average of sixty times per minute and in unison; their rhythm is controlled from the spinal cord with which they are connected by minute nerves. Some disturbances of rhythm, especially extrasystoles, have been produced in lymph hearts by experimental procedures.

Should the String Galvanometer Be Discarded for Clinical Electrocardiography?

None of the above discussion is presented with the idea that the apparatus and technic developed should immediately supplant those used at present. On the contrary, there are good reasons for continuing with present equipment for some time. In the first place, clinical service must be maintained without interruption. The interpretation of electrocardiograms is largely an empirical process, based on the accumulated evidence of many cases. Before a new technic can be of real value, we must establish for it a basis of comparison from which sound conclusions can be drawn. So far as general characteristics are concerned, the experience gained with the string galvanometer is fully available for the interpretation of these newer records, but new details have appeared and before they can be properly interpreted much clinical and postmortem data must be gathered.

Furthermore, it is highly desirable to maintain a standard method so that the published work of different men may readily be compared. Until a majority of workers have recognized the real advance that the introduction of the vacuum tube has made possible in the measurement and recording of small variations in electric current and voltage, and have adopted these later technics, string galvanometer records must be used as a medium for exchange of ideas and discussion.

Summary

The desirability of having better apparatus for electrocardiography is discussed. There are three major considerations:

1. The current which flows through the vibrating string of the Einthoven string galvanometer is not necessarily proportional to the potential differences set up during the heart beat.

2. The string galvanometer fails to respond adequately to important high frequencies. This is the most important major difficulty encountered with the string galvanometer.

3. The size of the record is suitable for qualitative analysis but not for accurate quantitative analysis of the phenomena studied.

A report is made of the further development of a new apparatus for electrocardiography. It consists principally of specially constructed vacuum tube amplifiers and a standard type of oscillograph. Records may be obtained with any two leads taken simultaneously.

A technic that amplifies and spreads out the electrocardiogram so that its full details may be seen is suggested.

A study is being made to determine the significance of the newly disclosed details of the electrocardiograms obtained by the new apparatus.

Satisfactory records have been obtained by the use of needle electrodes.

The new apparatus successfully records the potential differences set up by the beating of the minute lymph hearts of the frog.

The opinion is expressed that at present the Einthoven string galvanometer should not be discarded for clinical work. The technic of using the amplifier instrument must be firmly established and much comparative data must be collected before it can completely supplant the string galvanometer in electrocardiography.

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THE DIFFERENTIAL DIAGNOSIS OF DISEASES OF THE LIVER AND SPLEEN WITH THE AID OF ROENTGENOGRAPHY AFTER THE INTRAVENOUS INJECTION OF THORIUM DIOXIDE SOL (THOROTRAST): EXPERIENCE WITH EIGHTY PATIENTS*

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MANY REPORTS have appeared in medical literature within the last three years concerning results with a newly developed method of visualizing the liver and spleen. Einhorn and Stewart [1] were apparently the first to undertake the development of a method of this kind (1927). They made roentgen-ray films of the liver after the oral administration of tetraiodophenolphthalein and diiodoatophan and were able to demonstrate carcinoma and cirrhosis of the liver. The results, however, were not striking.

In 1928 Radt [2, 3, 4, 5] in his clinic at the University of Berlin, began work to develop such a method on the basis of the theory that a colloidal material of high atomic weight when injected into the blood stream might be taken up by the reticulo-endothelial cells and allow roentgenographic visualization of the liver and spleen, the two organs of the body containing the greatest number of these cells. A thorium dioxide preparation called tordiol was first tried by Radt and by the Japanese investigator, Oka [6, 7] but was discarded after use in animals because the solution was not stable and produced capillary emboli. Both men then turned to a somewhat similar preparation called thorium dioxide sol, which was found to be relatively harmless both in animals and in man. These investigators found that after the injection of this substance the size and contour of the liver and spleen were plainly visible; and in several cases they were able to determine the presence of metastatic carcinoma and of cirrhosis of the liver.

ANIMAL EXPERIMENTATION

A number of investigators have reported results of animal experimentation with thorium dioxide sol. The metal is removed from the blood stream several hours after intravenous injection by the cells of the reticulo-endothelial system in the liver, spleen, bone marrow, lymph nodes and to some extent in the lungs, heart, ovaries and adrenal glands. It is eliminated very slowly; in fact some of it may remain in the tissues for years. Various authors report different rates of elimination. The liver apparently loses the substance faster than other organs. Elimination may occur mainly through

* Read at the Montreal Meeting of the American College of Physicians, February 8, 1933.

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the bile and urine as indicated by the work of Leipert,[8] but apparently it may take place also by cellular transport to the lungs and be removed by the bronchial mucus as shown by Kadrnka[9] and by Irwin.[10]

Histologically the metal appears as greenish, refractive granules in the reticulo-endothelial cells, which appear globular and in which the nucleus is displaced to the periphery. The larger the dose the greater the engorgement of the cells.

Pathologic changes in animals thought to be due to the foreign substance have been reported by some investigators, but many have concluded that the damage is transitory or negligible. The work of Tripoli and Haam,[11] which has been personally followed to some extent by one of us (Yater), leads us to believe that in the dosage used in man there is no danger of direct injury due to the presence of the thorium dioxide in the tissues.

Lambin[12] studied the effect of injections in rabbits upon the blood picture. Moderate doses produced an erythroblastic reaction, while large doses produced a pronounced anemia, recovery from which was spontaneous. A phase of leukopenia followed the injections, but this changed to a longer phase of leukocytosis, first of granulocytes and later of monocytes. Popper and Klein[13] in similar experiments did not find changes in the blood picture of any importance. Thrombocytopenic purpura was produced in several rabbits by Shih and Jung[14] with doses of Thorotrast several times greater than those used in man. In this connection we have followed the platelet count in several of our patients following the injections, and have observed no significant changes.

The question concerning the effect of partial blockade of the reticulo-endothelial system by thorium dioxide sol on the immune reactions of the body to infection has been satisfactorily answered by Held,[15, 16, 17] by Vara-Lopez and Thorbeck,[18] and by Randerath and Schlesinger.[19] These workers concluded in the main that the presence of large amounts of the metal in the reticulo-endothelial cells has no very appreciable effect upon antibody formation, hemolysin titer, albumin-globulin coefficient, reciprocal storage capacity of the cells or in general upon the defense mechanism of the body against infection. One of us (Otell[20]) has reviewed the subject of the physiology of the reticulo-endothelial system and has pointed out the various probable functions of these cells. Apparently none of these functions is seriously or even moderately impaired by the method under discussion.

Radioactivity of Thorotrast *

The Council on Pharmacy and Chemistry of the American Medical Association[21] has recently not approved of the use of Thorotrast in man on the grounds of "very imperfect elimination, fairly high alpha-ray activity, the possibility of further increase in radioactivity by partial conversion to meso-

* Thorotrast is the trade name given by the Heyden Chemical Corporation to their stabilized, colloidal solution of thorium dioxide, which contains 25 per cent by volume of thorium dioxide. Thorotrast has been the preparation of thorium dioxide used by us and others for hepatosplenography.

thorium and radiothorium, and the possibility of sensitization of tissues to roentgen-rays." Seventy-five cubic centimeters of Thorotrast contain a quantity of thorium dioxide equivalent in alpha-ray activity to 1.5 to 3.0 micrograms of radium. The beta-ray and gamma-ray activity of this amount of thorium dioxide is probably too feeble to be of physiologic significance, but the alpha-ray activity is thought to be sufficient to be a potential source of danger when dispersed through the tissues. Proof of ill effects from this source, however, are thus far totally lacking, nor is there any published work which shows either that there is further increase in radioactivity with the passage of time or sensitization of tissues to roentgen-rays by Thorotrast. Radt [22] has observed no ill effects of any kind after three and a half years of extensive experience with Thorotrast both in animals and in man. Neither have we observed any changes attributable to the presence of Thorotrast in the tissues of patients after one and a half years. One patient with myeloid leukemia who has had seven roentgen-ray treatments during one and a half years following the injections of Thorotrast has remained in excellent condition and has not shown any evidence of sensitization to the roentgen-rays.

Reactions Due to Thorotrast

Reactions following the injection of Thorotrast into the blood stream have been few and mild. Occasionally there is a slight transitory discomfort, mild tension of the limbs, chilly sensations, or a moderate rise in temperature. Reactions attributable to the injection of Thorotrast occurred in only four of 80 patients on whom we used the method. A patient with Banti's disease complained of severe pain in the lumbar region and chest followed by spasmodic contractions of the recti abdominis muscles which subsided without residual symptoms or signs. Another patient complained of transient lumbar pain after the first injection. A child had some puffiness of the eyelids and face for three days. A fourth patient, who died as the result of hemorrhage from a traumatically ruptured spleen, had vomiting and transient collapse which may or may not have been due to the injection of Thorotrast.

Büngeler and Krautwig [23] reported a case of fatal rupture of an enlarged spleen occurring 22 hours after a second injection of Thorotrast. Many of our patients had enlarged spleens, but the only one who had a reaction was the one with Banti's disease.

Method of Administration

In adults of average size 25 cubic centimeters of Thorotrast are administered intravenously on each of three successive days. In children the dose is reduced roughly in proportion to the weight. More accurate estimation of dosage on the basis of body weight is apparently unnecessary. In general the density of the roentgen shadows of the liver and spleen depends upon

the quantity of the medium administered and the anatomical and functional integrity of the cells that store it. If only the outlines of the liver and spleen are desired the dose may be reduced one half. Fractional doses are used in order to eliminate the shock which might be produced by the injection of too large a dose of foreign material.

Films may be taken at any time after four hours following the last injection. On the night before the examination the patient is given the usual evening meal and at bedtime eight grams of compound licorice powder. On the morning of the examination a cleansing enema is given and the patient is instructed to come to the roentgen-ray department without breakfast. Films are taken in both the prone and supine positions on the Potter-Buckey diaphragm. The tube is centered over the ensiform cartilage. The following technic has been used in patients of the average physique: 60 K.V.P. at 100 m.a. for 3½ seconds at 25 inch distance. It is well in most individuals to place the film transversely in order to get a good image of the spleen and liver on the same film. A more comprehensive idea of the structural characteristics of the liver and spleen is obtained by making several exposures within a range of 10 K.V. of this dosage. Careful technic is essential in securing films which show details of structural change.

Normal Appearance and Size of the Liver and Spleen

In good films the liver should cast a homogeneous shadow of approximately the same density as the spine. The spleen normally has a density slightly less than that of the liver shadow, and about the same as that of the ribs. In some cases the kidneys are well visualized.

In determining whether the liver and spleen are abnormal in size it is necessary to know what the average normal size of these organs is. We obtained very little help from the literature in this regard, and unfortunately a sufficient number of individuals without alteration of the liver and spleen has not been studied to form a basis for this comparison. The only work of any value in reference to the size of the liver is that of Pfahler,[24] who compiled tables of the size of the liver in subjects of both sexes, of different ages and of varying heights and weights. These data were computed from flat films of the abdomen. Pfahler found that there was very little variation in adults in the size of the liver as determined roentgenographically. Two measurements of the liver shadow were taken; one was the "length" which was measured from the highest point of the upper border to the lowest border of the tip of the right lobe; the second measurement was made obliquely from the upper border to the lower border in a direction which gave the maximum measurement of the apparent thickness of the liver. The average normal length of the liver shadow was 21.3 cm., with limits of approximately 18 to 22 cm., and the average oblique measurement was 12.8 cm., with limits of approximately 10 to 14 cm. These data, while the best available, are obviously inaccurate because of the indistinctness of the liver

shadow in such films. The measurements were only comparative, inasmuch as the short distance between the tube and the film (25 inches) produced some distortion.

After the use of Thorotrast the right lobe of the liver appears to constitute most of the organ. The left lobe looks very small and is frequently obscured by the shadow of the spine. The left extremity of the liver rarely extends more than 6 cm. to the left of the midline. It comes to an acute angle under the left leaf of the diaphragm. The presence of ascites may give a false impression of the size of the liver, causing it to appear smaller than it should.

Comparative determinations of the size of the spleen are still more difficult since the spleen normally varies a great deal in size from time to time. Also, in normal subjects after the injection of Thorotrast the spleen may not be well visualized because of gas in the stomach. Even in cases of splenomegaly there may be some difficulty with this method in accurately determining the limits of the spleen for the same reason. Nevertheless, after experience with the method one may be able fairly accurately to estimate the size of the spleen, and changes in the size of the spleen in the same individual may be followed. The spleen may be considered to be of normal size if it occupies the space of two ribs and two interspaces. For recording our measurements we have used the greatest dimension and the dimension taken at a right angle to this through the middle of the organ.

Study of Cases

In November 1931 we [25] reported briefly on the study of this diagnostic method in eight cases. In this country Einhorn, Stewart and Illick [26] had just previously (July, 1931) reported their findings in nine cases. They [27] made a further report in January 1932 and stated that they had observed some severe but non-fatal reactions from the use of the method, one being hematemesis in a patient with Banti's disease and jaundice, which may have been due to the Thorotrast. In February 1932, Tripoli, Haam and Lehman [28] reported their use of the method in a patient and stated that they had not observed any reactions in 15 patients. We [29] presented our experience with the method in 40 cases at the annual convention of the American Medical Association in May 1932, stating that three non-fatal reactions had occurred. We are now reporting our experience with 40 more patients, a total of 80, with reactions in only four, as previously stated. All three groups of investigators commented upon the value of the method as an aid to diagnosis of diseases of the liver and spleen.

The 80 cases in our series included a number of conditions, but mostly they were instances of liver disease. Cirrhosis of the liver and metastatic carcinoma predominated. Of the 80 patients, 31 are known to have died in the natural course of their disease. Of these patients 19 came to necropsy; in 11 others, operation was performed and biopsy of the liver made

or splenectomy performed, while in seven more, operation was performed without biopsy. In 36 patients, therefore, an opportunity was afforded to verify the diagnosis. In many of the other cases the diagnosis was reasonably certain. It is felt that the value of this method of diagnosis can be fairly well vouchsafed from this study.

Cases in Which the Visualization Method Was Diagnostic

Cirrhosis of the Liver. There were nine cases of cirrhosis of the liver of Laennec's type in which the diagnosis could be positively made from roentgen-ray films alone. In three cases necropsy was performed. The size of the liver could be determined even when ascites made this estimation impossible by methods of physical diagnosis. In four cases the liver was shown to be smaller than normal, in two cases it was found to be enlarged, and in three cases it was apparently normal in size. Cirrhosis was indicated either by a diffuse mottling due usually to small, closely placed opaque areas (figure 1), or by much reduced density of a homogeneous liver shadow

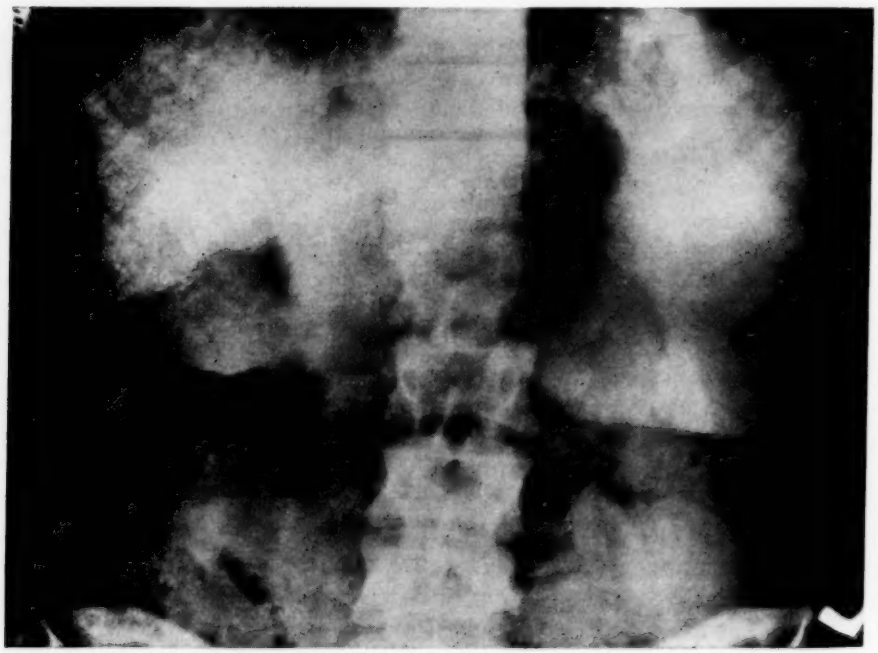

Fig. 1. Thorotrast film. Cirrhosis of the liver shown by small size of organ and mottling, associated with splenomegaly.

(figure 2). The small opaque areas are the islands of liver tissue remaining in the fibrotic organ (figure 3). The diminished density of the liver shadow in other cases is due to the fact that the fibrous tissue is not as great in amount or forms a finer meshwork. Also, the number of functioning

FIG. 2. Thorotrast film. Cirrhosis of the liver shown by greatly diminished density of liver shadow, associated with splenomegaly.

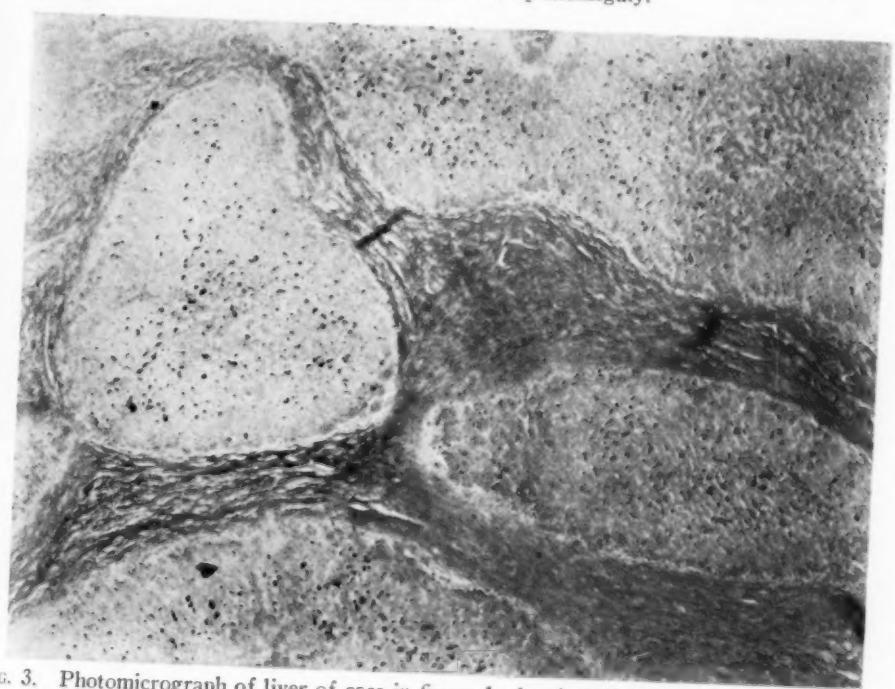

FIG. 3. Photomicrograph of liver of case in figure 1, showing islands of liver tissue containing Thorotrast (black spots) surrounded by fibrous tissue devoid of Thorotrast.

reticulo-endothelial cells in regenerated liver tissue may not be as great as in the original parenchyma. The spleen was shown to be moderately enlarged in eight of the cases; the density of the splenic shadow was normal. The presence of ascites was indicated in three cases by the presence of a space between the edge of the liver and the lateral wall of the trunk.

Metastatic Carcinoma of the Liver. The presence of metastases in the liver was definitely determined in 10 cases. Necropsy was performed in five cases, and a biopsy was made in one other. The liver was enlarged in eight cases, greatly so in some. The spleen was apparently not enlarged in any of the cases. Metastatic nodules appear as circular, relatively non-opaque areas, often surrounded by a narrow rim of density more opaque than the normal intervening parenchyma (figure 4). The appearance is

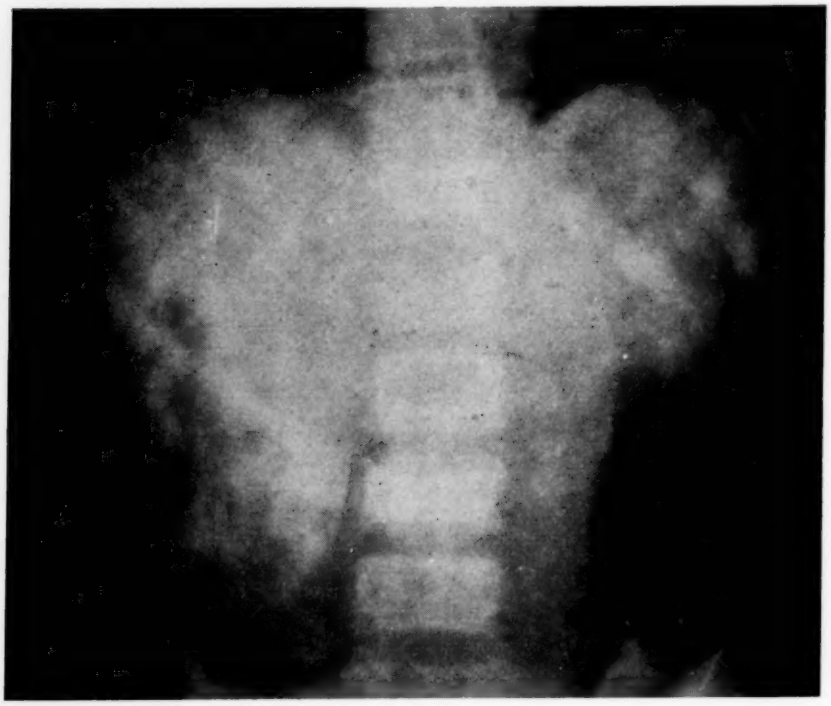

FIG. 4. Thorotrast film. Metastatic carcinoma of liver shown by multiple, large and small, non-opaque, circular areas surrounded by a halo of increased opacity in a greatly enlarged organ.

due to the facts that the cancer tissue has a poorly developed reticulo-endothelial structure and that compression of the surrounding hepatic tissue causes local concentration of the reticulo-endothelial units. The method may be of great value in cases of abdominal carcinoma when the question of advisability of operation arises. In some of these cases the patients were saved from an operation which would have been of no avail.

Syphilis of the Liver. Hepar lobatum could be diagnosed from the films alone in three cases. Necropsy was performed in one case. The blood Wassermann tests were strongly positive. This condition was indicated by enlargement, gross distortion and irregular, massive mottling of the liver shadow (figure 5).

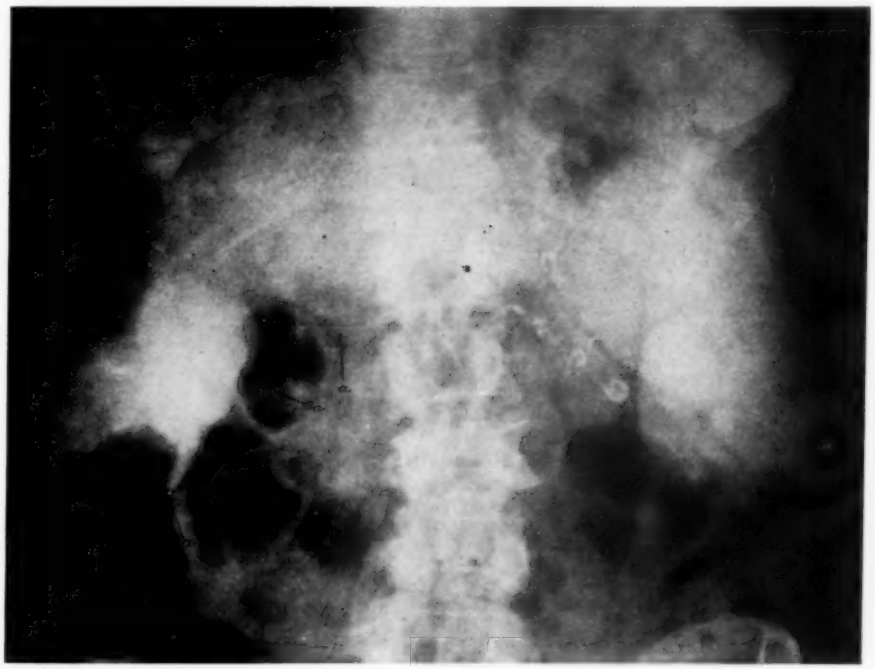

FIG. 5. Thorotrast film. Syphilis of the liver (hepar lobatum) shown by greatly distorted, grossly nodular organ, associated with splenomegaly.

Primary Tumor of the Liver. This diagnosis was made in two cases before operation and biopsy. In one case clinicians had thought that a large mass in the right side of the abdomen was a tumor of the kidney. A large, irregular area of diminished density in the liver was noted in the film. The halo of greater density such as that which surrounds a metastatic nodule was not present.

CASES IN WHICH THE NATURE OF A MASS WAS DETERMINED

In seven cases a mass was felt in the abdomen, the nature of which was uncertain on physical diagnosis alone. Necropsy was performed in two cases and operation in two others. In one case an indefinite mass in the upper left quadrant was shown by the test to be the spleen. In another case a mass in the left flank was shown not to be the spleen; it turned out to be an abscess in the abdominal wall. In a child with tuberculous peritonitis two large masses in the upper abdomen were demonstrated to be the liver and

spleen. The question of the nature of a mass in the upper right quadrant arose in a case in which it was found that the mass was not the liver, and in which operation revealed a high-lying appendiceal abscess. In one case a large mass in the upper right quadrant was thought to be liver, but the visualization method showed the liver to be normal, and the mass proved to be carcinoma of the kidney. In still another case a mass was felt in the upper abdomen which might have been the liver but which was proved by the visualization method not to be.

Cases in Which the Method Was Confirmatory of the Physical Diagnosis

In 13 cases enlargement of the liver and spleen, or both, was determined on physical examination. The diagnoses made in these cases were: acute catarrhal jaundice (1), Banti's disease (1), congestive heart failure (1), sickle cell anemia (2), purpura hemorrhagica (1), cured (?) leukemia (1), portal thrombosis (1), abdominal carcinoma (1), tuberculous lymphadenitis (1), no diagnosis (3). Necropsy was performed in two cases and splenectomy in one case. The visualization method merely confirmed the physical diagnosis. Structural alterations were not observed in the liver or spleen.

Cases in Which the Method Gave Suggestive Information When Compared with the Clinical Picture

In 11 cases the results alone of the method were not diagnostic but were of value when the clinical picture was considered in conjunction with them. Biopsy was performed in three cases and operation in one case. In another case the blood picture showed myeloid leukemia. In the six remaining cases confirmation of the clinical diagnosis was not obtained. Cirrhosis of the liver was diagnosed in five cases and proved by biopsy in two of them, metastatic carcinoma of the liver in two cases, hepatitis in one case which was proved by biopsy, myeloid leukemia in one case, ruptured spleen in one case in which operation had revealed a ruptured spleen that could not be removed, and primary carcinoma of the liver in one case. In the case of myeloid leukemia the splenic shadow was notably less dense than normally; reduction in its size was easily determined in subsequent films following roentgen-ray therapy. In the case of the ruptured spleen the normally sharp outline of the spleen was absent because of surrounding blood clots and gauze packing.

Cases in Which the Use of the Method Was Valuable in Ruling out Lesions

There were 12 cases in the series in which it was deemed desirable to determine whether there were lesions of the liver or spleen. Necropsy was performed in two of these cases and operation in two cases. In nine of the cases the use of the method showed that metastatic carcinoma was not

present in the liver. In two of these, operation was performed because of the absence of hepatic metastases, but it was unavailing in both cases. Splenomegaly was ruled out in one case and splenic atrophy in another (a case of sickle cell anemia). Rupture of the spleen was suspected in the case of a girl who was run over by an automobile; the spleen was shown to be normal and the patient recovered without an operation. The procedure may be of great value in such cases, since one injection of 25 c.c. of Thorotrast followed by the making of a roentgenogram in four hours may tell the story.

Cases in Which by the Use of This Method the Position of the Right Diaphragm Was Demonstrated

In two cases the right diaphragm appeared to be elevated in the flat roentgen-ray film, and Thorotrast was used to determine the position of the

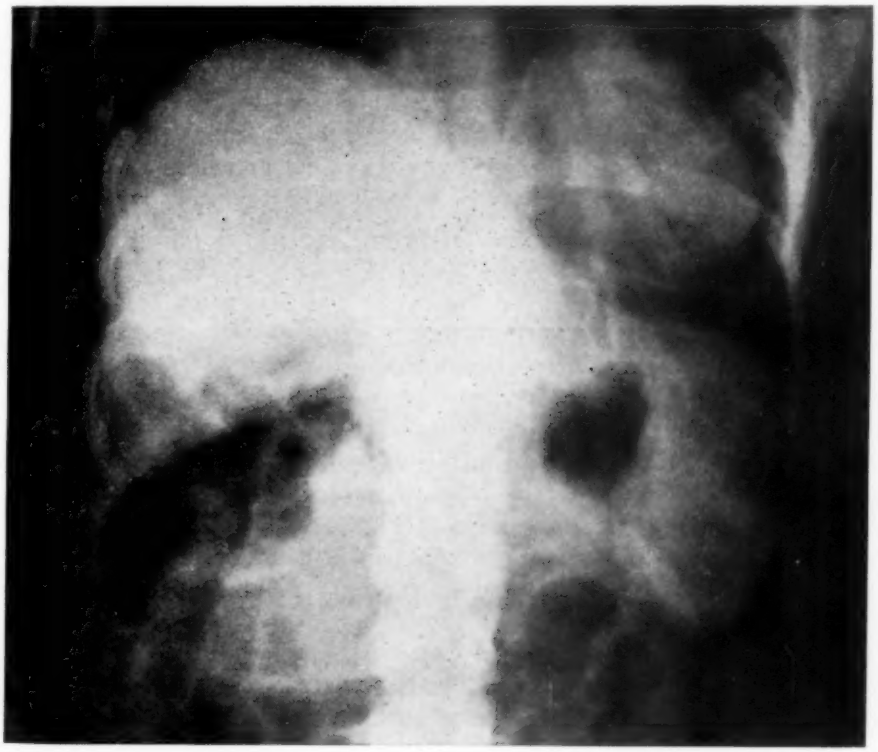

Fig. 6. Thorotrast film showing eventration of right diaphragm with elevation of the liver. Flat x-ray film had given a definite impression of subphrenic abscess.

diaphragm. In one case in which a subphrenic abscess was suspected eventration of the right diaphragm was demonstrated, the liver being merely elevated (figure 6); the fever was due to pelvic inflammation. In the other case it was shown that a lesion in the base of the right thoracic cage was the cause of the apparent elevation of the diaphragm.

Cases in Which the Method Was Employed for Scientific Information Only

In a case of xanthomatosis (Christian's disease) the procedure was carried out to determine whether the thorium dioxide would be taken up in the osseous lesions. It was not, and the spleen shadow was of normal density. A second case was one in which left hepatic lobectomy had been performed for amebic abscess. The film merely showed the absence of the left lobe, which apparently had not regenerated.

Cases in Which the Method Was of No Value or Was Confusing

In eight cases the films made after the injection of Thorotrast did not give any information of value for diagnostic purposes. In one other case the method was not only of no value but it caused the wrong diagnosis to be made. The roentgenographic diagnosis was metastatic carcinoma of the liver. There were large vacuolated areas in the liver. The case proved at necropsy to be one of biliary cirrhosis due to obstruction of the common bile duct. Long-standing obstruction of the common duct causes dilatation of the bile ducts, and it is probable that the appearance of the liver in this case was caused by this. In other cases of obstructive jaundice we have noticed linear, branched spaces in the liver which we interpreted as due to dilated bile ducts. This appearance may be helpful in determining whether jaundice is due to obstruction of the common duct or to intrahepatic disease.

Accessory spleens were visualized in several of the 80 cases of this series.

Conditions in Which the Method May Be of Value

In the following conditions the procedure may yield valuable information: (1) any enlargement or alteration of the liver the cause of which is not known, (2) the presence of a mass in the abdomen which might be the liver or spleen but the nature of which is uncertain, (3) suspicion of the presence of metastases in the liver in cases of carcinoma of an abdominal viscus when the question of operability arises, (4) the question of an abscess in the liver as the cause of sepsis when no other focus can be located after exhaustive study, (5) the desire to follow the progress of intrahepatic or splenic disease (made possible by the slow elimination of the metal), (6) the possibility of traumatic rupture of the liver or spleen, (7) the question of the presence of free fluid in the abdomen, (8) uncertainty as to the location of the right diaphragm, and (9) the presence of splenomegaly the cause of which cannot be determined by other procedures (the least valuable indication for the method).

Contraindications for the Method

In view of the uncertainty of the effect of alpha radiation by thorium dioxide and the possibility of remote conversion of some of the substance to a more radioactive preparation, we suggest that for the present Thorotrast

be used only for patients who are subjects of a rapidly fatal disease. In our experience there have been practically no contraindications for the use of the method from other standpoints. In the case of patients who have lived for many months after the injections there have been no apparent ill effects. Even extremely ill patients have not appeared to be harmed by the procedure, although moribund patients should naturally not be subjected to it. It is possible that the use of the method may be inadvisable in hemorrhagic conditions. Simultaneous severe liver disease and renal insufficiency has been deduced by Kadrnka[9] as a contraindication, since this author thinks that most of the Thorotrast may be eliminated through the bile and urine, and its continuous presence in the circulatory blood might be detrimental. Whether the latter is true or not, one would hardly desire to make use of the procedure in patients with such a serious condition.

Summary and Conclusions

A new method of visualization of the liver and spleen developed mainly by Radt and Oka is described. This consists of the intravenous injection of thorium dioxide sol, from which the radio-opaque thorium dioxide is engulfed by the reticulo-endothelial cells of the body. Since these are most numerous in the liver and spleen these organs are visualized better than other parts of the body. This method is a laboratory procedure and should in no way replace clinical methods of diagnosis. It may not be harmless, but except for the possibility of radioactivity contraindications are negligible. Reactions are few and are not serious. Eighty cases have been studied by us and the value of the method in this series has been discussed. The results alone of this method were diagnostic of the nature of lesions of the liver in 24 cases. Evidence suggestive of the nature of the liver or splenic disease was obtained in 11 cases. The nature of an undiagnosed abdominal mass was determined in seven cases. Confirmation of enlargement of the liver or spleen or both was obtained in 13 cases. The method was valuable in ruling out lesions of the liver or spleen in 12 cases. Supplementary information was obtained from it in 11 cases, so that a working diagnosis at least could be made. The position of the diaphragm was established in two cases. The method was of scientific value only in two cases. No aid was obtained from it in eight cases, and in one case the wrong diagnosis was made on the basis of the method.

The following points may be determined by means of this method: (1) the presence of enlargement of the liver or spleen, (2) decision of the question of whether a mass in the upper abdomen is liver, spleen or something else, (3) the presence of metastases in the liver, (4) the presence of a primary tumor, cyst, or abscess in the liver, (5) in many cases the nature and extent of such intrahepatic diseases as cirrhosis and extensive scarring of the liver from syphilis, (6) the progress of such diseases of the liver, (7) the presence of free fluid in the abdomen, (8) the existence of such lesions of the spleen as tumor, infarct, abscess, fibrosis and leukemia, (9) the exist-

ence of rupture of the liver or spleen, (10) the position of the diaphragm, (11) the presence of accessory spleens, and (12) possibly the presence of obstruction of the common bile duct.

As an adjunct to the previous methods of diagnosis the method is therefore of considerable value. Greater experience with it will reveal its true value, its finer points and its limitations.

The authors desire to express their appreciation to Major Virgil Heath Cornell, Curator of the Army Medical Museum, for the illustrations in this paper. Photographs of roentgen-ray films never do entire justice, however, to the details of the films, and the authors will be very glad to demonstrate the original films to those who may visit their clinic.

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SOME ASPECTS OF CELL PHYSIOLOGY *

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All agree that progress in medicine depends on accurate knowledge of the fundamental laws which govern all life processes. The study of these laws is the province of General Physiology, whose rise and development have been most gratifying, particularly since it has made use of the rapid advances of chemistry and physics.

In such studies it seems best to avoid the complexities of higher organisms and to attack first of all the simpler problems presented by single cells. This plan has met with a good deal of success, so that General Physiology is largely concerned with the study of the cell.

The significance of such studies for medicine is both theoretical and practical. Only through sound theory can medicine be saved from the blight of empiricism, the worst fate that could befall it. To theoretical studies we must always turn for clear insight into present problems, and for the inspiring vision of future conquests. Insofar as General Physiology succeeds in formulating a sound theory of living matter it will render to medicine a service of the utmost importance.

The application to medicine of the principles developed by General Physiology may not be immediate but in the majority of cases it is probable that it will eventually occur. I shall touch briefly on some instances of this in the course of my remarks.

Let me now call your attention to some cell studies which are of practical or theoretical interest.

Aside from pathogenic cells, the study of bacteria, of protozoa, and of other unicellular organisms is highly important. They not only reveal general laws which govern such organisms, but show apparent departures from these laws which are most suggestive in dealing with the pathogenic forms.

Such studies may yield specific methods of checking the parasite without injury to the host (as in chemotherapy and in radiation) and of controlling its dissemination outside of the body.

Observations on cells of the animal body are carried on in several ways.

A. Observations of erythrocytes, lymphocytes and other isolated structures, help us to understand the functions of the blood and lymph in health and in disease. Matters of importance to medicine, such as the absorption and giving out of materials by the erythrocyte, and the process of phagocytosis have been successfully studied in this way.

B. Certain eggs, especially those of cold-blooded animals, lend themselves readily to experiment and to microdissection which of late has made

* Read at the Montreal Meeting of the American College of Physicians, February 6, 1933.

From the Rockefeller Institute for Medical Research, New York, N. Y.

great advances. From such material came the discovery of artificial parthenogenesis and much of our knowledge of the physical basis of heredity.

C. In transparent tissues, as the ear of the rabbit and the tail of the tadpole, the growth of cells can be followed under the microscope. The behavior of lymphatics and of kidney cells can be directly observed in other animals.

D. Tissue cultures in vitro are most useful. Observations on the artificial production of overgrowths in such cultures are a case in point, likewise the effect of growth-inhibiting substances obtained from adult organisms, and the effects of roentgen-rays. Certain tissues of the kidney can be observed in this manner.

Comparison of animal and plant cells yields general laws of fundamental importance. An example is the conclusion that every living cell has a lipoidal surface. It follows that substances soluble in lipoid should be more readily absorbed by the cell surface (whether they pass from the surface into the body of the cell depends on other factors which have recently been pointed out in the " multiple partition coefficient " theory). This suggested a useful generalization regarding anesthesia, i.e., that substances like ether and chloroform are good anesthetics because they are soluble in lipoid materials and hence readily enter the cell surface.

Another example is found in physiologically balanced solutions. Certain animal and plant cells can live in distilled water but when we add sodium chloride it is toxic unless accompanied by the right amount of calcium. A solution containing salts in such proportions that the toxic effects of each are counteracted by the other is called a physiologically balanced solution. This explains the advantage of Ringer's solution over pure sodium chloride (physiological saline).

Physiologically balanced solutions are important for all kinds of cells. Recognition of this has led to improved clinical methods. Formerly the cerebrospinal canal was perfused with saline with disastrous results: these disappeared when a balanced solution was used.

The comparison of plant and animal cells has been useful in many ways. Thus it has been found that plants may be far more sensitive than animals to substances produced in blood and other body fluids under disease conditions so that such changes may be readily detected by making appropriate tests on plants.

I should like to mention one more example. General Physiology is much concerned with respiration as a fundamental activity of living matter. Accordingly a comparison of respiration in various types of cells becomes of interest. It has been found that the cells of malignant tumors have a very different respiration from the normal cells which surround them. Such a discovery is very significant.

Although many of these experiments were performed on excised tissues or even on whole animals of a very simple sort, the point of view in all cases

was that of cell physiology and the object was to arrive at the fundamental laws which govern living matter in general.

It should be emphasized that the application of physics and chemistry to medicine has come by way of General Physiology to a very large extent. Electrolytic dissociation and the Donnan equilibrium are good examples. The former is now too familiar to call for comment; the latter has found application in explaining the distribution of electrolytes in the case of erythrocytes and between blood and tissue fluids in edema.

It is not sufficient merely to study cells from the outside as in the experiments hitherto discussed. We need to get inside the cell in order to know what goes on there under a great variety of conditions. Ordinary cells are too small to permit this to a satisfactory degree for physiological purposes. But it is fortunately possible in the case of certain aquatic plants having cells larger than a pigeon's egg. Such cells can be kept alive for days while impaled on a capillary through which electric currents as well as various materials can be made to pass. This enables us to attack some fundamental problems which would otherwise be inaccessible. I shall deal more at length with this subject as it has not hitherto been placed directly before the medical public.

We employ two general methods which are made to check each other as far as possible:

1. Determination by chemical analysis of substances passing in or out of the cell and of processes occurring in its interior.

2. Measurement of the electrical changes which take place in the cell.

These methods have shown that these apparently simple cells are in reality exceedingly complex. They consist of a very thin layer of living matter (protoplasm) with a clear watery fluid inside (cell sap) and a firm cellulose wall outside. In spite of this simple structure they perform most astonishing feats.

We find, for example, that this thin layer of protoplasm (less than 1/250 of an inch thick) excludes some substances but acts as a trap for others, such as potassium, which may become forty times as concentrated inside the cell as outside. Hence it commonly happens that the fluid inside the cell (i.e., the sap) is very different from the sea water in which it grows.

Strange to say, when some of this sap is applied to the outside of the cell it soon causes death. This suggests that when animal tissues are crushed or injured, so that the internal fluids of the cell escape and come in contact with the outside of other cells, they may have a deleterious action. Whether certain cases of wound shock can be explained in this way remains an open question. It is stated that when a muscle is crushed deleterious effects are produced in other parts of the body if the blood is allowed to circulate through the injured part, but not otherwise.

In seeking an explanation of this we found that the electrical state of the cell is completely altered when sap is applied to the outside, for it creates a considerable electric potential directed from the outside of the cell to the

inside. This is in itself an interesting discovery for it shows that the very thin layer of protoplasm has an inner surface differing greatly from the outer. This has been confirmed in other ways. For example, when we apply certain toxic substances to the inner surface (injecting them through a capillary tube) the cell dies sooner than when they are applied to the outer surface. (The introduction of the capillary does not account for this result for it is introduced into every cell, including the controls.)

The electrical measurements are important in many ways. They enable us to detect even slight injuries, to measure the degree of injury and of recovery from injury, and to follow the process of death step by step. These methods are of especial value in the numerous cases where the cell retains its normal appearance after electrical tests show it to be dead.

We may thus hope to substitute measurements and quantitative concepts for such vague and unsatisfactory expressions as normal vitality, injury, recovery, and death.

If a small area of the cell be injured and we connect it electrically to an uninjured spot, we obtain the so-called "current of injury." Ordinarily the injured spot is negative but we have succeeded in making it positive and in thus reversing the "current of injury."

Certain of these plant cells behave electrically like muscle and nerve. When a muscle or a nerve is stimulated an electrical disturbance passes along it. Some plant cells give very similar electrical responses when stimulated electrically or by pressure, by reagents (including alcohol), or by change of temperature.

Such plant cells are highly desirable for experimental work because they act like single fibers of nerve or muscle. It is very difficult to obtain single nerve or muscle fibers for this purpose.

Just as the heart muscle sets up spontaneous rhythmic electrical disturbances which we record by means of the electrocardiogram, so do these plant cells, and they yield photographic records which are sometimes very much like those of the heart. The electrical disturbance which passes along the plant cell may perhaps be explained by the movement of potassium ions but this requires further investigation.

Pursuing the analogy we may recall that the nervous mechanism does not always function properly and that the causes are not well understood. It is therefore of interest that in plant cells certain reagents suppress for days at a time the normal electrical response after which irritability may be restored by changing the solutions bathing the cell.

It is of interest, too, to find that we can also bridge over a dead spot on the plant cell by making a "salt bridge" consisting of cotton moistened with saline. The electrical impulse will pass over this "salt bridge."

These electrical effects seem to depend on the presence of a non-aqueous layer at the surface of the watery protoplasm. The smallest break in this layer causes death, i.e., all the electrical effects disappear at once and substances can then pass in and out as they could not in a living cell. The dead cell may for a time remain chemically about as it was when alive.

This brings up the problem of the passage of substances into and out of the cell. In the living cell this exchange is restricted by the presence of the oily or lipoidal layer since only those substances soluble in it can pass through.

It seems possible that the presence of this non-aqueous layer together with the production of carbon dioxide by the cell may explain the accumulation of such substances as potassium in the cell. Most cells contain a much higher concentration of potassium than exists in the external solution which bathes them. We can bring about a similar state of affairs in an " artificial cell " with a non-aqueous surface provided we supply carbon dioxide to the interior.

Problems of medication and of nutrition are intimately allied to this study, which seeks to determine the mechanism by which all substances pass in and out of the cell. Examples of this will at once occur to you, such as the proper administration of iodine and of iron which can be given in a variety of forms. The problems of excretion and of secretion, especially of the kidney, should here be mentioned.

These artificial cells throw a good deal of light on the relation between the cell and its environment. It was formerly thought that a growing cell comes into approximate equilibrium with the solution bathing it. We now see that when the cell grows without changing its chemical composition it is due to a " steady state " in which water and electrolytes enter the cell in the same ratio, just as they do in the artificial cell. This " steady state " may be very far from an equilibrium.

It is a very interesting fact that we can imitate some of the characteristic electrical effects of the cell by means of such artificial cells. This has a good deal of significance because electrical effects play a special rôle in the study of living matter. It is often said that life phenomena must always elude us because they involve so many variables and especially because we change these variables to an unknown degree whenever we subject the organism to experimental treatment. But electrical methods detect such small departures from the normal that we may hope to minimize such unknown disturbances. And the use of single cells and of artificial cells enables us to analyze the effect of the single variables to a remarkable degree. If such studies can yield measurements of all the variables we may be sure that the analytical resources of modern science can deal with them satisfactorily. This should provide a rational basis for biology and for medicine.

EDITORIALS

ENTRANCE REQUIREMENTS

WHETHER or not such thorough-going reorganization of the practice of medicine as is advocated in the majority report of the Committee on the Cost of Medical Care ever is put into effect, it is evident that the relationships of the physician to his colleagues, to the hospitals, and to an increasing number of social agencies are destined to become closer and will constitute a larger part of his professional life. The relatively simple rôle played by the physician when he cares for a sick person single-handed is becoming restricted to cases of minor illness. In an increasing number of instances the doctor must work in conjunction with nurses, with laboratory specialists, with roentgenologists, with administrative and professional staffs of hospitals, and with consultants. Very frequently he finds himself allied with public health officials and with social service agencies. He is called upon for statements concerning his patients by charitable institutions, by insurance companies, by industrial accident commissions, and by various courts of law. The results of his examinations often determine fitness for athletic sports, the question of employment or of discharge from employment, suitability for matrimony, and even whether a criminal is to be hanged or hospitalized.

The physician's professional value today is dependent not alone upon his own knowledge and skill, but upon his wisdom and unselfishness in the choice of his collaborators and his ability to work in harmony with them. The physician's social value depends likewise not solely upon the grade of his professional attainments but upon those qualities of heart, of judgment, and of integrity which induce him to accept the rôle of arbiter which society so frequently thrusts upon him and to show himself worthy of the trust.

In these relationships with patients, with colleagues and with society, there is inherent a demand for absolute trustworthiness. In no other field of human activity perhaps is a man so frequently called upon to make decisions which are contrary to his own economic interests, or which involve the assumption of grave responsibilities, or which lead to the loss of sorely needed rest. If, then, the evolution of the medical profession is to increase still further the organization for medical care and integrate this organization even more closely with all the other social agencies of the community, how vital it is to the future of medicine that those admitted to its ranks should measure up well, not only to the intellectual demands which they must meet, but to the demands for character.

The medical schools, through their entrance requirements, hold in their hands the power to raise or to lower the standards of the medical profession of the future. The responsibility is a great one. It will not be met if admission to the medical school is granted on scholastic attainments alone.

It is not difficult to set up criteria of intellectual accomplishments which will eliminate most of the intellectually unfit; but it is exceptionally difficult to determine who will and who will not be worthy of trust. The selection of men for character as well as for ability is, however, a recognized necessity in many types of human organizations. This principle of selection should be openly adopted by our medical schools.

THE INFLUENCE OF THE ADRENAL CORTEX UPON SALT AND WATER METABOLISM

THE DEVELOPMENT of knowledge of the function of each of the various glands of internal secretion frequently runs a curiously similar course. Research into the nature of the rôle of such a gland in the body economy is usually followed along one of two lines which are well defined. The first involves the study of the effects of deficit, such as may be obtained by complete or partial removal of the organ in question, leaving the rest of the body, as far as possible, intact and uninjured. The second method consists in attempts to produce effects from replacement of the secretion in question either by gland transplant or by the elaboration of an active extract of the characteristic principle. Use of such a potent preparation will either make up the deficit produced by removal of the gland itself, or, if given in excess, may enable the investigator to observe the physiological effects of hyperfunction.

Speculation as to the possible function of a hormone whose action is not understood usually proceeds along one of two paths. The one considers the hormone to be an essential link in some more or less clearly defined metabolic activity, while the other is based on the theory that it has some detoxifying action. The second idea has been advanced to explain, at one time or another, the action of most of the known hormonal secretions, particularly during the period before a satisfactory preparation of the hormone itself has been isolated. The name *pituitary* suggests the ancient theory of its function—to rid the body of effete materials by way of the nasal secretions. The idea has recurred frequently, particularly as regards the secretion of the pancreas, that of the thyroid gland, and, most recently, regarding that of the parathyroids. As each hormone is isolated in a form sufficiently pure to enable satisfactory experimentation to be carried out without confusing side reactions due to the presence of impurities, the theory of detoxification in each case disappears. Since studies have been possible with the aid of parathormone, articles on guanidine tetany have disappeared from scientific periodicals.

The history of the study of the function of the adrenal cortex furnishes still another case in point. Until very recently the arguments of the proponents of a "detoxification" theory about evenly balanced those of investigators who considered that it fulfilled a specific metabolic function. Indeed, confusion has been so great that previous interpretations of the

most obvious clew were based on the theory of detoxification, which has proved to be quite erroneous. It has been known for nearly seventy-five years that removal of the adrenals, in the absence of accessory tissue, eventually causes death; the labors of a large group of investigators during the past two decades have proved that the " vital " portion of the gland is the cortex. Over the same period of time the observation has been made repeatedly that the injection of fluids containing salt will maintain the lives of animals deprived of their adrenals for periods several times as long as the survival periods of untreated controls. Stewart and Rogoff (1924), and Banting and Gairns (1926) have reported convincing experiments on dogs. Marshall and Davis (1916) and Corey (1928) have reported similar results in cats. Marine and Baumann (1927) found that not only physiologic saline solution or Ringer's solution, but sodium acetate as well, by daily intraperitoneal injection, were effective in prolonging the lives of adrenalectomized cats. Sodium glycerophosphate was less effective, but much more potent than glucose. They concluded that the sodium ion rather than the chloride ion was responsible for the favorable effect. Baumann and Kurland have particularly stressed the loss of chloride and of sodium from the blood plasma of the suprarenalectomized cat. Of the authors advocating the use of sodium chloride in the treatment of Addison's disease, Rogoff especially has stressed the importance of injections of physiological saline solution as an " indispensable aid " in the treatment of the acute manifestations, which are certainly very closely allied to the experimentally produced insufficiency. Nearly all of these observers, however, explained their findings on the theory of " detoxification "—a flushing out of poisons formed in the body as a result of normal or of perverted metabolism. The idea dies hard that some of the products of normal metabolism may be toxic and must be dealt with by a special means. It is by no means impossible that such may yet turn out to be the case, and that endocrine secretions may be involved, but each time the theory has been postulated in the past it has been disproved.

The similarity between the clinical picture of the crisis in Addison's disease, of adrenal insufficiency in the experimental animal, and of the general condition of " shock " is very striking. In the experimental adrenal insufficiency, blood concentration, loss of body weight and dehydration occur. Loeb has recently shown that a characteristic loss of sodium occurs from the blood and extracellular fluids, and that the loss takes place through the kidneys. Loss is possible through the gastrointestinal tract as in the shock produced by cholera or intestinal obstruction, as well as in the fluids lost into the tissues in traumatic shock, but neither of these routes is important in producing the loss of sodium, the dehydration, and the concentration of the blood in adrenal insufficiency. When injections of the cortical hormone are made into such an animal, the kidney threshold for sodium is again raised to the normal level, and the plasma electrolytes resume their normal concentrations. Loeb advances the opinion that the cortical hor-

mone regulates sodium metabolism just as parathormone regulates that of calcium.

The discovery of this regulation of sodium metabolism is of great significance. Investigation of the behavior of the inorganic constituents of the body fluids in recent years, particularly by Gamble, has indicated that the electrolyte concentration controls the amounts of fluids which the body contains. Loss of electrolytes inevitably produces loss of fluid as well. This must necessarily follow from the obvious conception that a stable osmotic pressure, as well as a stable temperature and acidity, is essential to the integrity of the living organism. Since it has been shown that the concentration of total base regulates the total concentration of electrolytes —which in its turn regulates the osmotic pressure—and since sodium accounts for 85 to 90 per cent of the total base of the blood plasma and extracellular water, the predominant rôle of the adrenal cortex in the regulation of the metabolism of salt and water, by reason of its control of the excretion of sodium can readily be appreciated. An interesting corollary to the effect of the cortical hormone upon salt and water metabolism is the fact that the hormone is powerless to relieve adrenal insufficiency in the experimental animal if sodium chloride or some other sodium salt is not provided at the same time in adequate amounts. Hetzel has shown that the plasma volume may drop about 50 per cent with the loss of sodium and chloride in the urine in adrenal insufficiency. The volume may double, on the other hand, if large amounts of the hormone are given intravenously, together with ample salt, but the result is not lasting. Other mechanisms appear to be able to counteract such an effect.

Recent studies have made much clearer the importance of adrenalin, the hormone of the adrenal medulla, in carbohydrate metabolism, the control of which it appears to share with insulin. The uncovering of the rôle which the other portion of the adrenal gland plays in the metabolism of salt and water indicates the fundamental importance of this organ in quite a different phase of the body economy. One or both of these functions may or may not have an intimate bearing on the less obvious and more subtle effects of adrenal dysfunction which clinical observations indicate exist in sex development and growth, and in the interaction of the other endocrine glands.

GEORGE A. HARROP

REVIEWS

Case Studies in the Psychopathology of Crime. By BEN KARPMAN, M.D., Psychotherapist, St. Elizabeth's Hospital; Professor of Psychiatry, School of Medicine, Howard University, Washington, D. C. 1042 pages. The Mimeoform Press, Washington, D. C. 1933. Price, $12.00.

This massive volume is the record of five cases seen by the author in Howard Hall, the Department for Criminal Insane at the federal psychiatric hospital under the superintendentship of William A. White, M.D., F.A.C.P., who has inspired much of the progress in the scientific treatment of criminals.

As the author states in his preface: "No apology is needed at present for any attempt to elucidate the problem of crime. Of all social problems it is undoubtedly the most pressing; of all the influences, the most demoralizing one. No economic expression of its cost, however high, can ever depict its present and far-reaching effect upon the community. The social, ethical, and above all individual psychic effects of crime go to the root of communal life and threaten it with destruction. Cancer-like it encroaches upon healthy living, normally functioning members, thriving at their expense, absorbing everything that may be useful to the social body but giving nothing in return."

This volume presents an excellent example of the ideal case history as presented from the patient's viewpoint supplemented by the opinion of his associates. Each history is presented in a scientific and systematic manner beginning with the official record which contains a brief statement of the patient's crime, his family history, his personal history, with detailed statement of his present illness, followed by the results of the psychiatric examination, physical findings, laboratory findings, and progress while in the hospital.

As the author states: "Many books written by criminals themselves while giving detailed accounts of how crimes are committed leave almost entirely unanswered the question of why the crime is committed. Routine psychiatric histories are in most cases quite unreliable and give only misleading pictures of the case."

As a method of bringing out the intricacies of the psychogenetic factors in criminal behavior, the author has had the patient present in autobiographical form, sometimes in a rather boresome manner, his own history. Psychoanalysis in any of its forms has been used only to a limited degree, and the author is apparently not arguing for psychoanalysis although he is an accredited practitioner of this art.

As the reviewer spent hours wading through ream upon ream, he was impressed with the scientific value of this type of case history. He could not recommend the book as light reading, except for its aphrodisiac effect, especially the lurid details of Case No. 3. In spite of the fact that details are not missing, the reader is not offended by the vividness of the experiences. One might at first criticize the voluminousness of these histories, but further consideration convinces the reviewer that the object of the author is only gained by such detail. As he himself states in the opening paragraph of the first case "the general type of information ordinarily obtained from a patient gives one but little clue to the vast pathology that may be involved."

No matter what the reader's theory may be as to the cause of crime, he will find within this volume a great deal of enlightenment, and he will be impressed with the need for more careful consideration of the psychogenetic factors in everyday life. "The criminal," after all, represents a member of society who has been caught. The internist meets in his practice every day potential criminals who through human interest and understanding may be prevented from anti-social behavior. Too much cannot be said in favor of careful consideration of the psychogenetic factors. Dr.

Karpman has not only contributed a valuable treatise to the as yet rather limited bibliography on the genetics of crime, but he has also contributed five case histories which will give any sincere physician a better understanding of human behavior. And since medical science has been asked to contribute its part to the solution of crime, it is well that more members of the profession become acquainted with the painstaking work that is being done by their confrères in this field.

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The Tides of Life. The Endocrine Glands in Bodily Adjustment. By R. G. Hoskins, Ph.D., M.D., Director of Research, Memorial Foundation for Neuro-Endocrine Research, Research Associate in Physiology, Harvard Medical School. 352 pages. W. W. Norton and Company, Inc., New York. 1933. Price, $3.50.

The author is a noted physiologist who has spent most of his professional life in research in the field of the internal secretions. His own work and interest and his editorial activities have given him a very broad knowledge of the tremendous literature of the subject.

It was no easy task that he set for himself, that of presenting in a semi-popular style "the more significant aspects of endocrinology as known today" without indulging too freely in its romantic temptations, but the author has succeeded very well indeed in giving a lucid, reasonably concise and sufficiently conservative exposition of his subject.

As might be expected he seems happier in his discussion of the laboratory features than in the clinical portions of the book and if certain critics take exception to the rather frequent inclusion in some chapters of "interesting speculations" they must admit that the author is usually careful to label them as such.

The book may be highly recommended to the audience for whom it is evidently intended, namely practitioners of medicine, students and intelligent laymen with an interest in biology.

T. P. S.

Anatomy of the Brain and Spinal Cord. By William W. Looney, A.B., M.D. Second Edition. F. A. Davis Company, Philadelphia. 1932. Price, $3.50.

This book is a concise description of the nervous system. The preface leads one to assume that it has been written as a text for medical students (the preface of the first edition is not included in this printing). If this assumption is correct it carries with it an obligation to develop the subject in a manner which is understandable to a beginner in the subject. To quote Dr. Looney: "It is suggested that the student familiarize himself with the external and internal configurations of the brain, as well as of the spinal cord, before undertaking the study of the tracts, as this will greatly facilitate his comprehension of them" (page 83). Then follows a systematic description of the long tracts of the cord throughout their entire course, both spinal and cranial, including many references to associated tracts and centers of the brain, none of which have received the slightest previous attention on the part of the author.

The meninges and blood supply are handled with the same disregard of the structures with which they are associated. The medulla oblongata, pons and midbrain are discussed in the order named. Finally, after a somewhat didactic discussion of the cranial nerves there follows a description of the cerebellum and forebrain. Throughout this narrative the most liberal reference is made to hitherto undescribed parts of the brain. Surely with a subject as inherently complex as that of neuro-anatomy, such an added handicap as this method imposes has little to recommend it.

The classification of receptors on the basis of their relation to the three primary germ layers appears to lack substantiation in fact. Neither exteroceptors, proprioceptors, nor interoceptors are confined to any one germ layer. It seems almost inconceivable that such an error as this could find its way into a textbook.

In his anatomical description the author is both concise and clear, but there is a conspicuous lack of reference to the phylogenetic relationships existing in the nervous system, a subject which is assuming more and more significance in medicine as is shown by the greater resistance to pathological processes exhibited by the more primitive structures as contrasted with the newer parts. The author has stressed the function of the various structures in a convincing manner and his brief explanation of the phenomenon of nerve degeneration is a happy inclusion which is seldom encountered in works of this kind.

A useful general bibliography is appended to the text.

C. L. D.

The Practitioner's Library of Medicine and Surgery. Supervising Editor: GEORGE BLUMER, M.A. (Yale), M.D., F.A.C.P.; David P. Smith Clinical Professor of Medicine, Yale University School of Medicine; Consulting Physician to the New Haven Hospital. *Volume IV: Nontraumatic Surgery.* Associate Editor: THEODORE S. MOÏSE, JR., B. A., M.D., Surgeon to the Eastern Maine General Hospital, Bangor, Maine. xlviii + 1146 pages, 335 illustrations. D. Appleton and Company, New York and London. 1933. Price, $10.00.

The first three volumes of *The Practitioner's Library of Medicine and Surgery* dealt, respectively, with Anatomy and Physiology as Applied to Practical Medicine, The Technic of Physical and Laboratory Examination in Clinical Medicine, and Practice of Medicine. The present volume (*IV, Nontraumatic Surgery*) contains sections contributed by twenty writers most of whom have been chosen because of special interest and experience in the fields which they have been asked to treat. Much inequality in completeness of presentation is evident in passing from one section to another; for instance, surgery of the pericardium and heart together occupy 57 pages while carcinoma of the prostate is allotted about 2. When evidences of compression in order to include such a wide field are so obvious, the wisdom of devoting space to surgical technic may well be questioned. Operative procedures are not to be learned from books. As a general reference work, the present volume will serve its purpose well. If it could have been developed as two volumes it would have been still more useful. The typography is excellent and the illustrations are well reproduced. Since this volume is of greater interest to the surgeon than to the internist, fuller description cannot be given here.

C. V. W.

Endocrine Medicine. By WILLIAM ENGELBACH, M.D., F.A.C.P., B.S., M.S., D.Sc.; Professor of Clinical Medicine, St. Louis University School of Medicine, 1911–24; Physician-in-Chief, St. John's Hospital, 1909–24; Member of Staff St. Louis, City, Jewish, Baptist Sanitarium, and Maternity Hospitals; President of Association for Study of Internal Secretions, 1922–23; President of the St. Louis Medical Society, 1918; Fellow of The American Medical Association and American College of Physicians, Member Missouri, Illinois, New York and Southern Medical Societies: with a Foreword by LEWELLYS F. BARKER, Professor Emeritus of Medicine, The Johns Hopkins University School of Medicine. Volume I, *General Considerations,* xxviii + 460 pages, 139 illustrations; Volume II, *The Infantile Endocrinopathies, The Juvenile Endocrinopathies,* xviii + 473 pages, 109 illustrations; Volume III, *The Adolescent Endocrinopathies, The Adult Endocrinopathies,* xxiv + 862 pages, 255 illustrations; Volume IV, *Bibli-*

ography, Index, 117 pages. Charles C. Thomas, Springfield, Illinois. 1932. Price, $35.00 for four volumes.

Review of *Endocrine Medicine* has been delayed awaiting the appearance of the fourth volume containing the Bibliography and the Index. During this interval came word of the death of the author. To his enthusiasm for his chosen field, his industry and thoroughness this work has become a very fitting testimonial. What better memorial can be conceived than that which makes it possible for a teacher, clinician, and investigator to record in permanent form the results of his endeavors and the conclusions derived from mature experience! Thus, much which would otherwise have perished with the man is preserved to be of use to others and to augment the totality of knowledge.

In the first volume of *Endocrine Medicine* are presented the essential general considerations such as gross and microscopical organology, and the physiology of the endocrine systems. The etiology of disturbances of function of the endocrine glands is then discussed from both extrinsic and intrinsic standpoints, and these chapters are followed by a series giving first the diagnostic procedures in the investigation of the endocrine state of the patient, and then a discussion of the endocrine reactions. This volume is concluded with chapters on the relation of the endocrinopathies to general medicine and to public health. The second volume is devoted to the infantile and juvenile endocrinopathies. Under the first division thyroid, hypophyseal, biglandular, gonadal, and parathyroid disorders are considered in the order named. For the juvenile endocrinopathies the order of presentation is much the same, the parathyroid section being replaced by one on the thymic syndromes. The third volume deals similarly with adolescent and adult endocrinopathies, 298 pages being devoted to the former and 563 to the latter. The fourth volume gives an extensive bibliography, by chapters, with alphabetical listing under each. This fills 51 pages, and is followed by detailed name and subject indexes.

Endocrine Medicine is the product of a courageous and successful attempt to put in orderly arrangement the content of this highly labile subject. It establishes routine procedures for investigating and evaluating the endocrine state of the individual. Throughout, it is very well illustrated and is replete with charts and tables for differential diagnosis. More than 2000 clinical case reports are utilized, many of them of patients who had been observed for more than ten years. Therapeutic procedures are discussed with a rational scientific conservatism which, too often, has been found wanting in this particular field. This set should have a place in every medical library, but it is of more than reference value. It gives the entire essential subject matter for the pediatrician or internist who is concerned especially in this field, and for all others engaged in medical practice of any description it provides a wealth of informative and stimulating material. Even with the lesser manifestations of endocrinopathy, there are certain inherent predispositions to diseases of other systems, knowledge of which places the practitioner in a strategic position in respect to differential diagnosis.

C. V. W.

Acidosis and Alkalosis. By STANLEY GRAHAM, M.D., F.R.F.P.S., Leonard Gow Lecturer on the Medical Diseases of Infancy and Childhood, University of Glasgow, and NOAH MORRIS, M.D., B.Sc., D.P.H., F.R.F.P.S., Lecturer in Biochemistry, University of Glasgow. Ed. I. xi + 203; 13 × 19 cm. William Wood and Company, Baltimore, Md. 1933. Price, $2.75.

In this small volume the authors have attempted to present a general survey of the fundamental concepts of acid-base equilibria as these are related to acidosis and alkalosis. This has been accomplished, and the mode of presentation is adopted to the understanding of the clinical reader.

The subject matter of the book falls naturally under three general headings. The first section deals with the reaction of the blood, the physical chemistry of carbonic acid and a survey and explanation of the terms to be employed in the following expositions. The second portion treats of the clinical applications of changes in acid-base equilibria in various types of disease. Diabetes, nephritis, gastro-enteritis, cyclical vomiting, ketosis, salicylate poisoning, anesthesia and other topics are discussed. The third part is in the nature of an appendix and embraces the ketogenic value of foods, the preparation of reagents and a discussion of normal and molar solutions.

In covering so wide a field the authors have been unable to treat these subjects with thoroughness or completeness. Nevertheless in each instance the important and often the most recent information on the subject has been satisfactorily presented.

It is to be regretted that throughout the volume, in chemical equations indicating the dissociation of electrolytes, the ions formed do not show their respective charges. The table on page 8 is antiquated. It is now generally conceded among physical chemists that strong electrolytes are more than 99.9 per cent dissociated in aqueous solution. In the chapter on the reaction of the blood nothing is mentioned concerning the nice difference in pH between arterial and venous blood.

On the whole the purpose of the authors as set forth in the preface, namely, to present the subjects of acidosis and alkalosis and their medical importance in a manner that will interest the clinician has been well fulfilled.

J. C. K., Jr.

Modern Aspects of Gastro-Enterology. By M. A. Arafa, M.R.C.P. (Lond.), Medical Assistant to Guy's Hospital, London, Medical Tutor to the Egyptian University and formerly senior medical registrar to Kasr-El-Ainy Hospital, Cairo. xvii + 374 pages; 17 × 23 cm. William Wood and Company, Baltimore. 1933. Price, $8.25.

The title, *Modern Aspects of Gastro-Enterology*, is in itself inviting; the compactness of the volume and the arrangement of material will appeal to those who have long wished for a brief treatise on Gastro-Enterology.

Though the author has chosen for discussion only some of the more important diseases of the gastrointestinal tract he has dealt with most of the other conditions in the sections on general methods of investigation and differential diagnosis. Nevertheless many subjects have received only brief mention in order to keep the size of the book within limits. The roentgen-ray plates illustrating certain of the commoner gastrointestinal abnormalities are excellent.

It is interesting that chronic gastritis, a disease the existence of which was disputed a few years ago, is accorded a prominent place in this volume. In view of recent advances in gastro-enterology it is fair to state that chronic gastritis deserves increasing attention and that the author has done wisely in recognizing this fact.

The author is cautious in accepting new forms of treatment and he admits frankly that such modern methods of therapy as Fogelson's mucin and Glassner's pepsin have not passed the experimental stage. The decided denunciation of the ambulatory treatment of peptic ulcer will come as a surprise to many of us although there can be no question that rest is of the greatest importance in the treatment of this condition. The author predicts that "the day is not far distant when we shall realize that, if adequate medical treatment of peptic ulcer fails and if there is a real indication for operation, anything short of gastrectomy is unlikely to result in a permanent cure of the patient."

The chapters on The Pancreas, The Simulation of Gastrointestinal Diseases and Practical Dietetics are excellent. The latter two chapters are especially good since they give the student information which is too little stressed in the ordinary medical curriculum.

Perhaps the fact that the author's experience has been obtained chiefly in England and Egypt accounts for his failure to refer to some of the more prominent names in American Gastro-Enterology. The index of subjects, too, could be more complete, and certain diseases, such as cancer of the stomach, deserve a fuller discussion. The influence of Hurst, with whose clinic the author was associated, is evident in many of the opinions expressed.

The book may be recommended as a valuable addition to the library of practitioners and of students of gastro-enterology.

S. M.

COLLEGE NEWS NOTES

The New York Academy of Medicine will conduct its Sixth Annual Graduate Fortnight, October 23 to November 3, 1933. The two weeks will be devoted to metabolic diseases. Many clinics will be given by Fellows of the College. Dr. Walter W. Palmer, New York City; Dr. Emanuel Libman, New York City, and Dr. Priscilla White, Boston, are Fellows of the College who will address evening sessions.

Acknowledgment has been made in these columns from time to time of gifts to the College Library of publications by members. The College has been engaged for some time in the collection of a library of books of which Fellows and Associates are the authors. The Library is maintained as a memorial to its members. Its usefulness and value, as well as sentiment, will increase as the College grows older. Recent contributions by the authors include:

Dr. O. H. Perry Pepper (Fellow), Philadelphia, Pa., and Dr. David L. Farley, Philadelphia, Pa.—1 book, "Practical Hematological Diagnosis";

Dr. John Favill (Fellow), Chicago, Ill.—1 book, "Outline of the Cranial Nerves";

Dr. H. M. Margolis (Associate), Pittsburgh, Pa.—1 book, "Conquering Arthritis";

Dr. William Gerry Morgan (Fellow), Washington, D. C.—2 reprints;
Dr. Julius P. Dworetzky (Fellow), Liberty, N. Y.—1 reprint;
Major Leon A. Fox (Fellow), Medical Corps, U. S. Army—1 reprint;
Dr. Frederick R. Taylor (Fellow), High Point, N. C.—4 reprints;
Dr. Philip B. Matz (Fellow), U. S. Veterans' Bureau—1 reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
Dr. William A. Groat (Fellow), Syracuse, N. Y.—2 reprints;
Dr. M. D. Levy (Fellow), Houston, Tex.—17 reprints;
Dr. W. R. Brooksher, Jr. (Fellow), Fort Smith, Ark.—2 reprints;
Dr. George W. Parson (Associate), Texarkana, Tex.—4 reprints.

Dr. Eugene E. Murphey (Fellow), Augusta, Ga., retired as Chairman of the Augusta Board of Health on June 9th, after serving for more than twenty-five years. Dr. Murphey is credited as being the first health officer in Georgia to recommend and use: tuberculin tests for dairy cattle; establishment of mosquito control; chlorination of the city's water supply; establishment of municipal laboratory; establishment of routine inspection of school children, and the practical elimination of rabies.

At the meeting of the National Tuberculosis Association at Toronto during June, Dr. Stuart Pritchard (Fellow), Battle Creek, Mich., was elected President and Dr. H. R. M. Landis (Fellow), Philadelphia, Pa., Second Vice-President. Dr. Kennon Dunham (Fellow), Cincinnati, Ohio, Dr. Willard B. Soper (Fellow), New Haven, Conn., Dr. James J. Waring (Fellow), Denver, Colo., and Dr. John H. Peck (Fellow), Des Moines, Iowa, were elected members of the Executive Committee.

The Fourteenth Annual International Medical Postgraduate Course given at Carlsbad this year with special reference to balneology and balneotherapy took place from September 10th to 16th. Lectures were delivered on the most important medical topics by eminent clinicians and surgeons of various countries. The United States of America was represented by Professor Max Einhorn (Fellow), New York City, and Professor Carl F. Cori, of St. Louis, Mo., who both addressed the Congress.

The Georgia State Medical Association, Emory University School of Medicine and the Georgia State Board of Health, in coöperation, offered a series of summer extension courses throughout the State during the summer. Dr. Cyrus W. Strickler (Fellow), Dr. James E. Paullin, Jr. (Fellow), and Dr. Stewart R. Roberts (Fellow), all of Atlanta, gave the courses in medicine.

Dr. Mary O'Malley (Fellow), Washington, D. C., was installed as President of the Medical Women's National Association at its meeting in Milwaukee during June.

Under the presidency of Dr. Seale Harris (Fellow), Birmingham, Ala., the Chattahoochee Valley Medical Association held its Thirty-Third Annual Session at Albany, Ga., July 11th to 12th. A number of the Fellows of the College contributed to the program.

Dr. Ernest S. duBray (Fellow), San Francisco, Calif., and Dr. Mark L. Gerstle, Jr. (Associate), San Francisco, Calif., were recently advanced to the rank of Associate Clinical Professor of Medicine and Assistant Clinical Professor of Neurology, respectively, at the University of California Medical School.

Dr. Hugh S. Cumming (Fellow), Washington, D. C., Surgeon General of the U. S. Public Health Service, was the recipient of the honorary degree of Doctor of Laws from Yale University.

Dr. William B. Castle (Fellow), Boston, Mass., Assistant Professor of Medicine at Harvard University Medical School and the 1933 recipient of the John Phillips Memorial Prize given by the American College of Physicians, recently received the honorary degree of Master of Science from Yale University.

Dr. Robert O. Brown (Fellow), Santa Fe, N. M., has been elected President of the New Mexico Tuberculosis Association.

Dr. John A. Toomey (Fellow), Cleveland, Ohio, has been advanced to Associate Professor of Pediatrics at the Western Reserve University School of Medicine, Cleveland.

A portrait of Dr. Henry A. Christian (Fellow) Boston, Mass., was presented to the Peter Bent Brigham Hospital at a dinner in May. Dr. Christian is Professor of the Theory and Practice of Physics and Physician-in-Chief to the Peter Bent Brigham Hospital.

Dr. Joseph F. Bredeck (Fellow), St. Louis, Mo., is Health Commissioner of the City of St. Louis, having assumed his duties on April 20th last.

Dr. Delivan A. MacGregor (Fellow), Wheeling, W. Va., is now President of the West Virginia State Medical Association.

The West Virginia Heart Association was organized during May. The officers are Dr. Oscar B. Biern (Fellow), Huntington, President, Dr. George H. Barksdale (Associate), Charleston, Vice-President, and Dr. Raphael J. Condry (Associate), Elkins, Secretary.

Dr. Paul J. Connor (Fellow), Denver, Colo., has been elected President of the Colorado State Board of Health.

Dr. William H. Robey (Fellow), Boston, Mass., has been elected President of the Massachusetts Medical Society.

Dr. Jacob J. Singer (Fellow), St. Louis, Mo., Associate Professor of Clinical Medicine, Washington University School of Medicine, and Dr. George H. Hoxie (Fellow), Kansas City, Mo., President of the Missouri Tuberculosis Association, have been named members of a committee to make a survey of tuberculosis control problems in Missouri.

Dr. B. B. Vincent Lyon (Fellow), Philadelphia, Pa., and Dr. Russell S. Boles (Fellow), Philadelphia, Pa., were elected first Vice-President and Secretary, respectively, of the American Gastro-Enterological Association at its last annual meeting.

Dr. John T. King, Jr. (Fellow), Baltimore, Md., was reëlected Secretary of the Congress of Physicians and Surgeons of North America at the last meeting of that board.

Dr. John A. McIntosh (Fellow), San Antonio, Texas, has been elected President of the Texas Neurological Society for the ensuing year.

Dr. John Zahorsky (Fellow), St. Louis, Mo., has been appointed Director of the Department of Pediatrics of the St. Louis University School of Medicine.

Dr. Mary M. Spears (Fellow), Philadelphia, Pa., was recently elected the first woman member of the American Proctologic Society.

Dr. William deB. MacNider (Fellow), Chapel Hill, N. C., Professor of Pharmacology in the University of North Carolina Medical School, has been elected President of the American Society for Pharmacology and Experimental Therapeutics.

Dr. Alvin G. Foord (Associate), Pasadena, Calif., has assumed the duties of President of the American Society of Clinical Pathologists. Dr. Frederick H. Lamb (Associate), Davenport, Iowa, has been elected President-Elect.

Dr. LeRoy S. Peters (Fellow), Albuquerque, N. M., has been elected President of the American Sanatorium Association and a Director-at-Large for two years of the National Tuberculosis Association.

OBITUARIES

DR. WILLIAM HENRY MERCUR

Dr. William Henry Mercur died at his home, in Pittsburgh, on July 16, 1933, at the age of seventy-two years. Dr. Mercur was born in Towanda, Pennsylvania, on January 19, 1861, the son of Mahlon Clark Mercur and Anna Hubbard Jewett Mercur. After completing his preliminary education he entered the University of Pennsylvania School of Medicine from which he graduated in 1883. Later he pursued postgraduate studies in England, France, Germany and Switzerland, and then entered upon the practice of medicine in Pittsburgh.

Dr. Mercur was a member of the teaching staff of the Western Pennsylvania Hospital and College from 1883 to 1893, and of the Nurses Training School, Southside Hospital, from 1893 to 1910. He was a Founder and a Staff Member of the Pittsburgh Diagnostic Clinic from 1926 until his death.

He was a Fellow of the American College of Physicians from the time of its organization. He was a member of the Allegheny County Medical Society, the Pennsylvania State Medical Society, the American Medical Association, the American Climatological and Clinical Association, the American Therapeutic Society, the Association for Research in Nervous and Mental Disease and the American Association for the Advancement of Science. He was a member and, in 1901, President of the Pittsburgh Academy of Medicine.

Since 1911 Dr. Mercur limited his practice to consultation work. He devoted much of his time and energy to social and public health problems. He early took an active part in widening the effectiveness of the city department of public health, and was responsible for instituting the use and availability of diphtheria antitoxin in the Pittsburgh district. He established and maintained at his own expense a library of medical and surgical reprints, probably the most complete in the country, which was freely available to any physician. His system of medical nomenclature and indexing of diseases is in use in many hospitals throughout the United States. He was deeply interested and largely instrumental in the organization and development of the Pittsburgh Diagnostic Clinic, the purpose of which is to render the highest type of medical service to persons of moderate means.

Dr. Mercur, during his entire professional career, occupied an important niche in the medical and civil life of the community. He was a regular attendant upon medical meetings, deeply interested in all the problems of scientific medicine and of medical practice, and he will be greatly missed by a wide circle of friends.

E. Bosworth McCready, M.D., F.A.C.P.

DR. ROLAND E. LOUCKS

Dr. Roland E. Loucks died of cardiac disease at his home, in Detroit, Michigan, on June 5, 1933. He had been in ill health for about two years but recently, after several months of confinement, he had recovered sufficiently to take care of his practice.

Dr. Loucks was born at Smith Falls, Ontario, in 1869. After attending the schools of his native town he matriculated into the University of Maryland where he studied dentistry, obtaining the degree of D.D.S. in 1893 when he was awarded the Gold Medal. He practiced dentistry for several years, after which he entered upon the study of medicine at Trinity University, Toronto, graduating in 1903. Dr. Loucks located in Detroit where he practiced his profession for thirty years. About 1912, Dr. Loucks be-

came interested in radiotherapy, directing his attention particularly to radium. He later used both radium and the x-rays. To qualify for his chosen specialty, he spent the year of 1914 in postgraduate study in London and Berlin. He became known and recognized both in the United States and Canada as a radiotherapeutist. He was one of the founders of the American Radium Society of which he was at one time president. He contributed extensively to the literature of his chosen specialty.

Dr. Loucks was a member of the American Roentgen-Ray and Radium Society, the Radiological Society of North America, a Fellow of the American College of Physicians, member of the Wayne County, Michigan State and American Medical Associations. He was radium therapist to Harper Hospital, Detroit, from 1916 to 1926. In 1926, he built and equipped the Memorial Hospital of which he was director until his death. During the years that Dr. Loucks confined his attention to a specialty he was a familiar figure at the annual meetings of the various national medical societies of which he was a member.

He is survived by his wife, one son and one daughter. He was a man not only of wide medical experience but of broad sympathies. He developed a sustaining philosophy of life that insured him a wide circle of intimate friends.

JAMES D. BRUCE, M.D., F.A.C.P.

DR. JUDD CAMPBELL SHELLITO

Dr. Judd Campbell Shellito (Fellow), Independence, Iowa, died in Cedar Rapids, April 16, 1933, of injuries sustained in an automobile collision that day. His death was due to a basal skull fracture, with probable internal injuries. An occupant of the other car in the collision was also killed. Dr. Shellito was returning from Council Bluffs, where he had attended the spring meeting of the Iowa Clinical Medical Society, of which he was Secretary-Treasurer.

Dr. Shellito was born in Independence, Iowa, May 25, 1889. He attended high school at Pasadena, Calif., and at Evanston, Ill. He graduated from Princeton University in 1911, and from Johns Hopkins University School of Medicine in 1915. His internship was served at the Harper Hospital, Detroit. In 1917, he enlisted in the U. S. Army Medical Corps, and was stationed for some time at the Cook County Hospital, Chicago, and later at Fort Riley, Kansas. He served with the American Expeditionary Forces in France for a year and a half, having charge of the X-Ray Department of Hospital No. 3 in Paris. After the war, he returned to Independence, and became associated in the partnership of Drs. Shellito and Agnew.

He was a member of the Buchanan County Medical Society, the Iowa State Medical Society, the Iowa Clinical Society, the Austin Flint Cedar Valley Medical Society, the Iowa X-Ray Club, the Radiological Society of

North America, a Fellow of the American Medical Association and a Fellow of the American College of Physicians since 1931.

He was also active in civic affairs, being a past President of the Rotary Club, on the local Boy Scout court of honor, and a Trustee of the First Methodist-Episcopal Church. He was long active in the management of the People's Hospital, being a member of its Board of Directors and of its Executive Committee.

"Dr. Shellito was an outstanding factor in his community, a man of action in varied fields, professional, religious, social and civic. . . . In his activities for his church, in the medical societies with which he was affiliated, and in his membership of other organizations, he gave of his best, devoting time, finances and of his talents to bring to success any undertaking he assumed. He had the courage of his convictions; he was, perhaps, blunt in speech, but always open and aboveboard, without subterfuge, always working for the best as he saw it. A man of innate honesty of purpose and ability, he was an asset to the community and in any movement in which he had a part."

ELMER G. SENTY, M.D., F.A.C.P.

DR. THOMAS WRAY GRAYSON

Dr. Thomas Wray Grayson (Fellow) died May 17, 1933, at his home in Pittsburgh, of cerebral hemorrhage. Dr. Grayson was born November 22, 1871, at Meadeville, Pennsylvania. He attended the Meadeville and Washington High Schools and received his B.A. and M.A. degrees from Washington and Jefferson College. In 1897 he graduated from the Western University of Pennsylvania Medical School, served his internship at the West Penn Hospital and after postgraduate courses in New York and Berlin, began the practice of medicine in Pittsburgh, specializing in internal medicine. His death removes from the profession and the community an active and valuable member. Deeply interested in civic affairs, Dr. Grayson took a prominent part in the activities of the Civic Club of Pittsburgh and acted as Chairman of several committees which were largely instrumental in the installation of medical inspection and open-air classes in the public schools. A devout churchman, he was a communicant of the Church of the Ascension and a trustee of the Episcopal Diocese of Pittsburgh.

He was a member of the American Legion, the Officers Reserve Corps, the Military Order of the World War, and belonged to the University and Sojourners Clubs and the Phi Gamma Delta Fraternity. He was elected to Fellowship in the American College of Physicians in 1920. He was a member of his county and state societies and of the American Medical Association. He was also a member, and one time treasurer, of the American Gastro-enterological Society. At the time of his death he was on the staffs of the Presbyterian Hospital and the Protestant Home for Incurables.

E. BOSWORTH MCCREADY, M.D., F.A.C.P.